



The Immunoglobulin A and Interleukin-6 Levels of “Biosmart and Safe Bus” and Regular Bus Passengers

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Abstract. The inhalant increasing risk of transmission in public transportation, is buses. Biosmart and safe bus apply the principle that the bus compartment which is a biological environment must be in a balanced state according to the disease triangle concept that is influenced by the host, in this case is the passenger, the agent causing the infection is a virus and the environment is the room in the bus cabin. The aim of the present study is to analyze the differences in IgA and IL-6 levels of Biosmart and safe bus passengers and regular bus passengers. This research is a non-blinded randomized control trial with pre-posttest design. Seventy passengers were randomly separated into two groups. Control group ($n = 35$) uses regular bus, and intervention group uses Biosmart and safe bus ($n = 35$). Nasal wash was taken by ENT specialists, and the levels of Sinonasal IgA and IL-6 were interpreted by ELISA. The data were analyzed by using Mann Whitney, Wilcoxon, Independent t-test and Paired t-test. The results is sinonasal IgA level got significant increase in all groups, respectively on pretest-posttest of intervention group $17,89 \pm 30,19$ ($p = 0,021$), control group $30,18 \pm 76,09$ ($p = 0,014$) while the delta IgA level on control group and intervention group resulted in no significant difference ($p = 0,182$). The IL-6 level also increased in all groups with significant difference ($p = 0,000$), the delta resulted in significant difference ($p = 0,013$) with intervention group $13,38 \pm 0,96$ and control group $13,90 \pm 1,27$. Interleukin-6 sinonasal levels of Regular Bus and Biosmart and Safe Bus passengers show difference with higher

levels on regular bus passengers. Meanwhile, the delta IgA levels of Regular Bus and Biosmart and Safe Bus passengers are not different from the increase level of the two.

Keywords: biosmart and safe bus · interleukin-6 · immunoglobulin-A · sinonasal level

1 Introduction

Immune system is one of the most dynamic systems that we have in our body. The humoral and cellular immune balances are in a state of potential homeostasis in the face of injury. Mechanisms that maintain immune homeostasis must face various conditions such as cell proliferation and the death of cells in the body [1]. Air pollution has various health effects. The health of vulnerable and sensitive individuals can be affected even on days when air pollution is low [2]. Pollutants that are the main factors causing disease in humans include, Particulate Matter (PM). Particulate matter can penetrate the respiratory system through inhalation, causing respiratory, cardiovascular, reproductive, central nervous system dysfunctions, and cancer [3, 4]. Particulate matter includes nitrogen oxides, sulfur dioxide, Volatile Organic Compounds (VOCs), dioxins, and polycyclic aromatic hydrocarbons, all of these components are considered as air pollutants that are harmful to humans [3, 5].

Modes of transportation, such as cars and buses, use fossil fuels that come from high emission sources. Particulate matter can be released directly from the engine or formed through chemical reactions from primary pollutants [4]. Several other factors such as aging, body temperature, drugs, pathological conditions such as allergic rhinitis and environmental factors such as the presence of pollutants, smoke and dust can affect the NMC system. Any dysfunction in this defense system can increase the inflammatory process and stasis of airborne pathogens, and the respiratory system becomes susceptible to disease and obstructive airway infections [7]. The inflammatory response to acute PM exposure is primarily characterized by increased IL-6 secretion [6]. The increase in CO (340 g/m³) concentration occurred in 6–11 h and NO₂ (15.9 g/m³) in 0 h–24 had a close relationship in the occurrence of an increase in plasma IL-6 levels [5]. The sinonasal immune system plays an important role in carrying out host-protective defense functions and immune homeostasis between commensal microbiota and invading pathogens. The main component of the immune system that acts on the mucosal area is immunoglobulin A (IgA), which is the predominant immunoglobulin in the mucosa. In previous studies, it was stated that IgA levels increased in acute infection and inflammation [8].

IgA examination is more effective in the upper respiratory tract by using a nasal wash sample, while IgG is more effective in the lower respiratory tract by serum examination. Nasal wash sampling technique can be used as an indicator of the composition of nasal IgA so that it can contribute as an indicator of protection for the upper respiratory system [9]. The greatest risk for infectious disease in public modes of transportation such as buses is people sitting or standing close together in a closed environment. These vehicles can be a significant source of pollutants and microorganisms when passengers do not cover their mouths when coughing and sneezing [10]. The concept of Biosmart and safe

buses means that buses as public transportation provide services for passengers who adopt the concept of adapting new habits in an effort to prevent the spread of disease due to inflammatory lesions [11]. The concept of Biosmart and safe bus aims to minimize the risk of injury (agent) in the closed environment/bus cabin as a risk of exposure to injury in a component of the bus [12]. Closed bus compartments cause the risk of exposure to pathogens, which can be in the form of pathogenic microorganisms or toxic compounds produced due to pollution exposure to the respiratory organ system which is the first organ system that comes into direct contact with the environment [12, 13].

2 Materials and Methods

This study is a quantitative study, the research design is Quasi experimental pre and posttest randomized control trial by comparing between two groups, namely the control group and the intervention group with inclusion criteria: the subject is willing to sign the informed consent, the subject is in good health, the subjects are students from Diponegoro University who are apprentices and trainees of matching fund Biosmart and safe bus, and the subject have a covid-19 vaccine certificate. The exclusion criteria were that the subject consumed alcohol during the study period, the subject smoked during the study, the subject was pregnant or menstruating and the subject used an inhaler during the study. A total sample of 70 participants were obtained from the inclusion criteria, and were divided into 2 groups (randomized sampling): Biosmart and safe bus treatment group ($n = 35$) and regular bus ($n = 35$) with a minimum travel time of 21 h. Participants were subjected to a pretest sampling using the nasal wash method. After that, the post-test sample of participants was taken after the participants traveled with the same method as the pre-test method.

Sampling using a nasal wash was carried out by an ENT-KL specialist with the subject sitting in a sitting position with the head extended 45 °C. Subjects were instructed to take a deep breath and hold their breath, a syringe containing 20 ml of distilled water was inserted into one nose, while the other nose was closed. The subject was then instructed to look down and slowly drain the fluid into the reservoir. The procedure is repeated in the other nostril. The procedure is carried out two times pretest and post test.

Preparation of Biosmart and safe bus with the process of making a bus prototype is by arranging a 1-1-1 seat to adjust the seat distance between one passenger and another which aims to maintain physical distance. Air circulation is regulated to form a laminar air flow, the application of HEPA Filter technology, UV-C lamps and the use of Nano silver technology on all surfaces of the Biosmart and safe bus cabin. The whole process is carried out by CV Karoseri Laksana, Semarang.

Elisa test with analysis of IgA and IL-6 levels were obtained from nasal wash samples (immediately before and after the trip). Sampling was done by instructing the respondent to sit with the head extension 45 °C. Participants were asked to take a deep breath and then hold it. A total of 20 cc of aquabidest at 37 °C was injected into the right and left nasal cavities and then instructed to bend down and slowly drain the liquid into the reservoir. Nasal wash samples were stored at 4 °C for further examination using the ELISA method. ELISA examination for IgA and IL-6 levels used Human IgA ELISA Kit 96 wells ABCLONAL RK00200 and Human IL-6 ELISA Kit 96 wells ABCLONAL RK00004 96 wells.

All data were analyzed using SPSS version 26. The distribution of IgA and IL-6 data was tested using the Shapiro Wilk method. Primary data resulting from IgA and IL-6 measurements were analyzed using Mann-Whitney, Wilcoxon, Kruskal Wallis, paired T and Independent T tests according to group type. Trend analysis is assessed by making a mathematical trend formula for delta/difference in IgA and IL-6 levels to see the trend in the direction of the graph.

The study had received approval from Health Research Ethics Committee the Faculty of Medicine Diponegoro University with number 412/EC/KEPK/FK-UNDIP/XI/2021.

3 Results

Subjects were obtained from participants who passed the inclusion and exclusion criteria as many as 70 participants. Analysis of participant characteristics was assessed based on age, body mass index, temperature, alcohol history, medical history and smoking history (Table 1).

Immunoglobulin A and Interleukin-6 Level, based on (Table 2) the results of descriptive data on IgA levels obtained data normality $p < 0.05$ in the regular bus group and Biosmart and safe bus so that the data distribution is not normal (Fig. 1).

From Table 3, the results show that the average difference in IgA levels in the regular bus and Biosmart and safe bus groups has increased between pre-test and post-test. This mean difference shows statistically significant results with $p = 0.000$ in the pretest and $p = 0.002$ ($P < 0.05$) for the post test in the regular bus group and the Biosmart and safe bus group. The pre-test and post-test values of the regular bus group and the Biosmart and safe bus group show a significant difference test with a value of $p = 0.014$ for regular

Table 1. Demographic data of participants by group

Variable	Bus		P
	Regular	Biosmart	
Age	20,43 ± 1,04	20,94 ± 1,00	0,055 [‡]
BMI	22,39 ± 3,16	22,77 ± 4,04	0,856 [‡]
Temperature	35,59 ± 0,77	35,71 ± 0,56	0,874 [‡]
Alcohol history	2 (50)	2 (50)	1,000 [£]
Comorbid			
autoimmune history	0 (0)	0 (0)	–
liver, lungs, heart disease history	0 (0)	0 (0)	–
malignant disease history	0 (0)	0 (0)	–
hereditary disease history	0 (0)	0 (0)	–
Pregnant/menstruating	0 (0)	0 (0)	–
Smoking	3 (33,3)	6 (66,7)	0,477 [¥]

Explanation: [‡]Mann whitney; [£]Fisher’s exact; [¥]Pearson chi square

Table 2. Descriptive and normality of IgA pre-test, post-test and delta

IgA	Bus	Mean ± SD	Median (min–max)	p [€]
Pre-test	Regular	91,32 ± 56,07	77,34 (24,01–204,57)	0,000
	Biosmart	49,50 ± 15,76	45,53 (26,99–83,72)	0,011
Post-test	Regular	121,50 ± 79,48	95,04 (31,89–308,33)	0,001
	Biosmart	67,40 ± 33,95	58,73 (25,73–143,03)	0,022
Delta	Regular	30,18 ± 76,09	30,12 (–150,2–217,6)	0,720*
	Biosmart	17,89 ± 30,19	16,51 (–27,12–95,71)	0,018

Explanation: *Normal (p > 0,05); €Shapiro-wilk

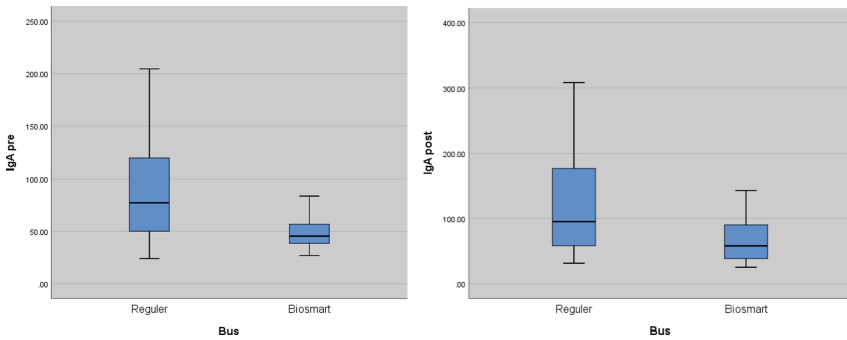


Fig. 1. Boxplot median IgA levels pre and posttest using bus

Table 3. The difference between IgA pre-test, post-test and delta.

IgA	Bus		P
	Regular	Biosmart	
Pre-test	91,32 ± 56,07	49,50 ± 15,76	0,000 [‡] *
Post-test	121,50 ± 79,48	67,40 ± 33,95	0,002 [‡] *
P	0,014 [†] *	0,021 [†] *	
Delta	30,18 ± 76,09	17,89 ± 30,19	0,182 [‡]

Explanation: *Significant (p < 0,05); [‡]Mann Whitney; [†]Wilcoxon

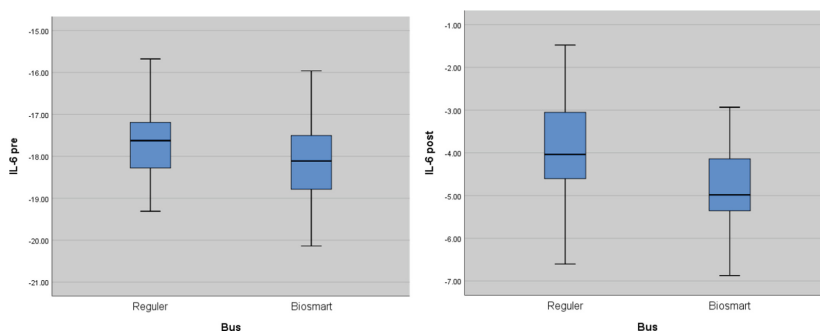
buses and p = 0.002 for Biosmart and safe buses. Based on the results of the examination of IL-6 levels, the data normality is p > 0.05 in the regular bus group and the Biosmart and safe bus in the pre-test and post-test so that the data distribution was normal (Table 4 and Fig. 2).

From Table 5, the results show that the average difference in IL-6 levels in the regular bus group experienced an increase between pre-test and post-test and the Biosmart and safe bus group also experienced an increase in IL-6 levels. This mean difference shows

Table 4. Descriptive and normality of IL-6 pretest, posttest and delta

IL-6	Bus	Mean \pm SD	Median (min-max)	p [€]
Pre-test	Regular	-17,72 \pm 0,92	-17,62 (-19,31-(-15,68))	0,203*
	Biosmart	-18,15 \pm 1,10	-18,11 (-20,14-(-15,96))	0,675*
Post-test	Regular	-3,83 \pm 1,21	-4,04 (-6,60-(-1,48))	0,676*
	Biosmart	-4,77 \pm 0,95	-4,98 (-6,87-(-2,93))	0,284*
Delta	Regular	13,90 \pm 1,27	14,32 (10,54-15,60)	0,013
	Biosmart	13,38 \pm 0,96	13,46 (10,58-15,20)	0,085

Explanation: *Normal ($p > 0,05$); [€]Shapiro-wilk

**Fig. 2.** Boxplot median IL-6 levels pre and posttest using bus**Table 5.** Differences in IL-6 pre-test, post-test and delta

IL-6	Bus		P
	Regular	Biosmart	
Pre-test	-17,72 \pm 0,92	-18,15 \pm 1,10	0,083 [§]
Post-test	-3,83 \pm 1,21	-4,77 \pm 0,95	0,001 [‡] *
P	<0,000 [¶] *	<0,000 [¶] *	
Delta	13,90 \pm 1,27	13,38 \pm 0,96	0,013 [‡] *

Explanation: *Significant ($p < 0,05$); [§]Independent t; [‡]Mann Whitney; [¶]Paired t;

that the results are not statistically significant with p value = 0.083 in the pretest and significant with $p = 0.001$ ($p < 0.05$) in the post test, so there is a significant difference for the post test in the regular bus group and Biosmart and safe buses. The different test values for pre-test and post-test show statistically significant results with p value = 0.000 in the Biosmart and safe bus and regular bus groups so that it is found that there is a significant difference between Biosmart and safe buses and regular buses in the IL-6 response.

4 Discussion

The study was conducted in two groups, namely the group of participants who boarded the Biosmart and Safe Bus and the control group, namely the participants who boarded the regular bus. The Biosmart and Safe Bus concept is an engineering bus cabin that creates laminar air circulation and places a HEPA Filter and UV-C, nanosilver coating on all cabin surfaces and the use of herbal masks on the host so as to reduce the risk of exposure to both fine particle pollutant compounds, pathogens, microorganisms and other compounds [13].

Immunoglobulin A is one of the humoral immunity which has a role in host defense against pathogens [14]. IgA antibodies are produced by the immune system in response to the presence of various pathogens such as bacteria, viruses or other pathogens that infect the body, an increase in IgA responses can have an effect due to the presence of pathogens that infect the body. On regular buses, there is a significant increase in the amount of IgA between pre-test and post-test compared to the amount of IgA increase which tends to be normal in subjects who ride the Biosmart and safe bus [15].

Interleukin-6 is a pro inflammatory cytokine that plays an important role in the pathophysiology of an infection by stimulating macrophages and neutrophils to produce a number of reactive oxygen species (ROS) and cytotoxic [16]. Serum IL-6 can respond to acute inflammatory reactions and be one of the early indicators of an infection. A previous study found that IL-6 has better sensitivity and specificity compared to conventional inflammatory indicators such as C-Reactive Protein (CPR) [16].

The results showed that both groups experienced an increase in IL-6 in the post-test compared to the pre-test, while the results of the comparison of IL-6 levels between Biosmart and safe bus passengers were significantly different from regular bus passengers with higher levels on regular buses. Interleukin-6 acts as a pleiotropic cytokine with multiple roles in immune response, tissue repair and regeneration. Rapid regeneration of IL-6 may contribute to host defense during tissue injury and pathogen infection, while over-synthesis and large accumulation of IL-6 can lead to pathology disease [17]. Therefore, it can be said that IL-6 has a dual role in the on-off system in controlling inflammation [18].

The difference in IL-6 delta results obtained in the regular bus group compared to the Biosmart and safe bus is influenced by several factors, including the concept used in laminar air circulation in the Biosmart and safe bus can reduce pathogenic injury which can prevent a higher increase in IL-6 levels, lower than the increase in IL-6 levels on regular buses. This study is in line with research on the difference between turbulent airflow and laminar airflow applied to hospital operating rooms [19]. The laminar air flow technique is proven to be more efficient inhibiting the spread of bacteria compared to turbulent air flow [19].

HEPA Filter technology, UV-C lamp and the application of nanosilver that coats the surface of the cabin are also other factors that can affect the difference in IL-6 levels on regular buses and Biosmart and safe buses. HEPA Filter is an air purification filtering technology against small particles including bacteria and viruses in the air with a filtering percentage of 99.97% [20, 21]. In addition to air filters, UV-C lamp technology is applied to Biosmart and safe buses, shown to inhibit the transmission of viruses and bacteria

>99% to 100%, but the study also explained that the number of organisms killed by UV-C lamps can decrease when the relative humidity increases [22].

Nano silver is considered to be the most commonly used engineered nanomaterial and has many benefits such as antimicrobial properties, water and air filtering, as a biosensor and in vivo biomarker in diagnostics. [23] In a study by Rostami, et al. in 2021, it was proven that the effectiveness of paint combined with silver nanoparticles in reducing the level of fungal contamination in hospital wards proved to be effective compared to paint without nanoparticle combinations. [24] In another study also explained that very small nano silver particles ($d_p < 10$ nm) easily release ions from the oxidized surface which dominate the antibacterial performance. So that the effect of applying nano silver to the entire cabin of the Biosmart and safe bus buses can inhibit the increase in IL-6 compared to regular buses without the application of nanoparticles [23].

Apart from differences in air circulation, HEPA Filters, UV-C lamps and the application of Nanosilver in the cabin of the Biosmart and safe buses, another factor that affects the difference in results in IL-6 levels is the presence of social distancing which is applied to the concept of passenger seating of Biosmart and safe bus. The inhibition of increasing levels of IL-6 Biosmart and safe buses compared to regular buses proves that the effect of social distancing can reduce the spread of infectious pathogens. This research is in line with research that shows that physical distancing and compliance can slow down the transmission of the virus with varying effect time lags [25]. In another study regarding the effect of social distancing with the spread of infectious diseases, it was found that social distancing can reduce the spread of infectious diseases (viruses) and slow down the rate of infection and death [26].

Factors Affecting IgA and IL-6 Levels, 1) Length of journey, In land transportation modes such as buses, the length of the trip is one of the factors that affect the levels of IgA and IL-6. The longer the duration of the journey, the physical condition will decrease so that it will be easier for pathogens to infect [27]. In addition, people sitting or standing close together in a closed environment have a great risk of transmitting disease. The spread of pathogens or other inflammatory injuries such as pollutants can be one of the risks faced by passengers in bus transportation modes. Biosmart and safe buses with engineered healthy pathobiological concepts can reduce the risk of pathogens and pollutants [10]. 2) Smoking Habit Cigarette smoke increases inflammation by inducing the production of pro-inflammatory cytokines, such as TNF-, IL-1, IL-6, IL-8 and granulocyte-macrophage colony-stimulating factor (GM-CSF), and increases the accumulation of immune cells in the airways, such as IgA [28]. Smoking habits can also cause a ciliotoxic effect so that it can reduce the genesis of cilia, and weaken the ciliary beating activity (CBF) and reduce the number of cilia [7]. In addition, smoking habits can cause changes in the respiratory mucosa of the respiratory mucosa in a metaplastic manner by increasing the size and number of goblet cells, causing an increase in the production of excessive airway secretions [7]. 3) Gender and Age, Gender and age can affect IgA levels in a person. Serum IgA levels are lower in young women than in young men [29]. Salivary IgA levels were significantly higher in adults than in children. The average salivary IgA level increases with age up to 60 years and then decreases slightly at 61–70 year [30].

5 Conclusion

Interleukin-6 sinonasal levels of Regular Bus and Biosmart and Safe Bus passengers show difference with higher levels on regular bus passengers. Meanwhile, the delta IgA levels of Regular Bus and Biosmart and Safe Bus passengers are not different from the increase level of the two.

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