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Immunogenicity of COVID-19 Vaccines in the Upper Respiratory Tract: A Comparative Study of Pfizer-BioNTech and Johnson & Johnson Vaccines among Ugandan adults

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Abstract

COVID-19 vaccination has been shown to elicit robust systemic immune responses against SARS-CoV-2. However, little is known about vaccine-induced mucosal responses in the upper respiratory tract (URT), particularly in sub-Saharan Africa. Here, we characterized nasal immune responses among Pfizer-BioNTech and Johnson & Johnson (J&J) COVID-19 vaccine recipients in Uganda.

Overall, we observed a significant increase in the proportions of CD8 + T cells in the nasal mucosa ($p = 0.0500$) and peripheral blood ($p = 0.0484$). Additionally, CD8 + tissue-resident memory (T_{RM}) T cells identified by co-expression of CD69 and CD103, showed an increased abundance in the upper respiratory tract ($p = 0.2469$), accompanied by a simultaneous decrease in their proportions in blood ($p = 0.0300$) following vaccination.

Comparison of immune responses between the two vaccine groups at 4 weeks after the first vaccination dose for Pfizer and only dose for J&J revealed significantly higher immune cell counts of CD45+ ($p = 0.0182$), CD3+ ($p = 0.0136$), CD4+ ($p = 0.0091$), and CD8+ ($p = 0.0182$) T cells among J&J recipients compared to Pfizer-BioNTech. Furthermore, J&J recipients showed a significantly higher abundance of CD4 + CD69+ T_{RM} cells ($p = 0.0182$) compared to Pfizer. Conversely, proportions of SARS-CoV-2 specific nasal CD8 + T cells expressing IFN-γ, Perforin and TNF were higher among Pfizer recipients four weeks after the first dose. On the other hand, J&J recipients revealed significantly higher CD8 + IFN-γ+ ($p = 0.05$) and CD107a+ ($p = 0.05$) responses at week 12 compared to Pfizer group. Taken together, our findings demonstrate the induction of nasal T-cell responses to COVID-19 vaccination in Ugandan volunteers, with notable differences observed between the J&J and Pfizer-BioNTech vaccine platforms. These data highlight the need to better understand mucosal immunity to COVID-19 and other vaccines, especially in low- and middle-income settings.

Introduction

The rapid global spread of SARS-CoV-2 in 2019–2022 resulted in the urgent development and deployment of effective vaccines, including mRNA-based vaccines such as Pfizer-BioNTech BNT162b2 and adenovirus-vectored vaccines like Johnson & Johnson/Janssen Ad26.COV2.S(J&J) (1–3). Despite this prompt innovation, significant disparities in vaccine access emerged globally during the COVID-19 pandemic, with Africa bearing a disproportionate burden mainly due to limited local manufacturing capacity, logistical challenges, and advance purchase agreements by high income countries (4–6). This inequity resulted in slower vaccination rates across the continent, highlighting the vulnerabilities in global health equity and significantly impacting pandemic control efforts in underserved regions (7). While these vaccines have demonstrated significant production of systemic humoral and cellular immune responses against SARS-CoV-2 (8, 9), local immunity in the upper respiratory tract is increasingly recognized for its crucial role in controlling early viral replication and preventing transmission to the lungs. (10, 11). Therefore, understanding the kinetics and tissue localization of

SARS-CoV-2-specific vaccine-mediated immune responses to different vaccine platforms is crucial for deciphering protective immunity.

Studies have reported immune responses elicited by COVID-19 vaccines, with mRNA-based vaccines being the most studied (12, 13). These have revealed significant increases in anti-spike protein antibodies, including neutralizing antibodies against the original SARS-CoV-2 strain and several variants of concern such as Alpha, Beta, Gamma, Delta, and Omicron (14–16). Furthermore, these vaccines have also been shown to trigger strong T-cell responses, crucial for viral clearance and long-term immunity (17). In a similar regard, adenovirus-vectored vaccines, such as Oxford-AstraZeneca and J&J, have also been shown to induce both systemic and mucosal immunity against SARS-CoV-2 (18, 19). Moreover, these vaccines elicit robust and durable humoral and cellular immunity, including neutralizing antibodies and T-cell responses against the SARS-CoV-2 spike protein (20). However, like most intramuscularly delivered vaccines, most COVID-19 vaccines have demonstrated limited mucosal immunogenicity, including minimal mucosal IgA or resident memory T cell induction in the upper respiratory tract (21, 22).

Although intranasal COVID 19 vaccines did not receive emergency use authorization during the pandemic, some have demonstrated high efficacy in phase 2 and 3 clinical trials (23, 24). A key goal of these vaccines is to trigger strong mucosal immune responses to block pathogen entry and replication. The nasal cavity is rich in lymphoid tissue, which can induce both humoral and cellular immunity, thus exerting a broad spectrum of protective effects (25, 26). For instance, Bharat Biotech's intranasal vaccine (BBV154) showed strong serum neutralizing antibodies and higher salivary IgA levels than intramuscular vaccines, indicating enhanced mucosal immunity (27).

Our group and others have shown that both vaccination and natural SARS-CoV-2 infection led to the expansion and maturation of tissue-resident T cells in the upper respiratory tract, alongside robust systemic and mucosal antibody responses (28–31). While mRNA vaccines elicit stronger humoral responses in blood, cellular immune responses have been found to vary between vaccine platforms, highlighting the importance of monitoring both arms of immunity to comprehensively evaluate vaccine efficacy (32). Additionally, in cases of breakthrough infection, virus-specific nasal-resident CD4 + and CD8 + T cells have been detected (33), further emphasizing the critical role of local T cell immunity in the upper respiratory tract. However, the immunogenicity of vaccines, including those for COVID-19, is known to be influenced by geographical and demographic factors (34, 35). Therefore, studies in African populations such as in Uganda, where data remain limited, are crucial for understanding immune responses in settings with unique environmental exposures and genetic backgrounds. (36, 37).

In this study, we compared the SARS-CoV-2-specific T cell responses induced by the Pfizer-BioNTech mRNA vaccine and the Johnson & Johnson adenovirus-vectored vaccine in the upper respiratory tract (nasal cavity) and systemic (peripheral blood) compartments of adult vaccine recipients in Uganda.

Methods and materials

Study design

This was an immunogenicity sub-study nested in a larger study entitled “Progressive Immune Response and Prevalence of False Positivity of endemic diseases antibody RDTs following COVID-19 vaccination in Uganda.” The aim of the parent study was to describe the immunogenicity and reactogenicity of various COVID-19 vaccines in Uganda. In addition, we aimed to determine if HIV, hepatitis C, and malaria antibodies cross-react after the vaccination and the duration of such cross reactivity.

Study participants and settings

Ugandans aged ≥18 years seeking COVID-19 vaccination at Kiswa Health Center IV in Kampala were invited to voluntarily participate in this study. All participants provided written informed consent, and subsequently, a comprehensive demographic questionnaire was administered at enrolment.

Sample collection and processing

From all consenting participants, a nasopharyngeal (NP) swab and ~ 8ml of blood (BD ACD Vacutainer) were collected at three time points: before vaccination (baseline V00), at 4 weeks (V01) after the first vaccination and 8 weeks (V02) after the second vaccination for Pfizer /12 weeks after only dose for J&J (**Fig. 1A)**. NP swabs were collected using COPAN FLOQSwabsR (COPAN-CE0123), placed in 3ml of Viral Transport Media (VTM) on ice and processed within 4 hours of collection. At the Uganda Virus Research Institute – International AIDS Vaccine Initiative Program lab, swabs were processed as previously described (28), while peripheral blood mononuclear cells (PBMCs) were processed from whole blood samples via density gradient centrifugation.

Antigen-specific stimulation and Flow cytometric staining

Freshly isolated nasal cells and thawed PBMCs were stimulated for 16–20 hours (37°C, 5% CO2) with 1 µg/mL of variant-specific SARS-CoV-2 Spike peptide pools (PepTivator, Miltenyi Biotec). To evaluate responses against then-circulating Omicron lineages, we utilized mutation-specific pools (BA.1, BA.2, and BA.4/BA.5) consisting of 15-mer peptides with an 11-amino-acid overlap selectively covering mutated Spike protein regions (**Supplemental Table 1**). Co-stimulatory antibodies antiCD49d/CD28 ((BD Biosciences), a protein transport inhibitor containing monensin BD GolgiStop™ (BD Biosciences), and anti–CD107a (clone H4A3, BD Biosciences) were added to the stimulation cocktail. Following stimulation, cells were stained with Live/Dead Fixable Aqua viability dye (Invitrogen), permeabilized with fixation/permeabilization solution (eBiosciences) and subsequently stained with both surface and intracellular cytokine dyes in the dark for 30 min at 4°C using an optimized panel of fluorochrome-labeled antibodies (**Supplemental Table 2**). Stained cells were then acquired using a BD LSRII flow cytometer (BD Biosciences).

Data analysis and visualization

Immune cell phenotypes were interrogated using FlowJo version 10.9.0 (Becton Dickinson Life Sciences), as illustrated in the gating strategy (**Fig. 1B**). Non-parametric Mann-Whitney tests and linear mixed models were deployed to compare changes in log10-transformed nasal immune cell abundance

(typically cells/swab) and T cell frequencies that were background subtracted. In these models, visit and vaccine type (as categorical variables) were the main predictors. Specifically, visits 2 and 3 were compared to baseline, and comparisons were made between vaccine types. All statistical analyses and visualizations were performed using SPSS v27 (IBM® Inc.) and Graphpad Prism version 10 (GraphPad Software, LLC) respectively.

Ethical approval

Ethical approval to conduct the study was obtained from the Uganda Virus Research Institute Research and Ethics Committee (UVRI-REC), approved on August 10th, 2021. All participants underwent a written informed consent process. Privacy and confidentiality were upheld during the recruitment, collection of data and storage and the study followed the guiding principles of the Declaration of Helsinki.

Results

Study participant demographics

Twenty-one participants with a median age of 27 (IQR,22.5-32) years were enrolled into the study prior to receiving their first vaccine dose. Of these, 66.7% (14/21) were followed up at week 4 post-vaccination (Visit 1, V01), and 42.9% (9/21) were followed up at week 12 (V02); 8 weeks after the second vaccination for Pfizer (Visit 2, V02) representing a 33.3% and 57.1% loss to follow-up at Visit 1 and Visit 2, respectively (**Table 1, Fig. 1A**). At baseline, 71% (15/21) of participants were male and 29% (6/21) were female; most (14/21, 66.7%) received the Pfizer vaccine (**Table 1**).

Table 1 : Study participant baseline demographic characteristics

Age Median (IQR)	**27 (22.5-32)**
Sex	Male (n=15) Female (n=6)
Vaccine type	Johnson & Johnson (J&J) n=7 (33.3%) Pfizer-BioNTech n =14 (66.7%)
Follow up	4 weeks (V01) (14/21, 67%) 12 weeks (V02) (9/21, 43%)

Phenotypic characterization

Upper respiratory tract immune cell profiles were characterized using an optimized flow cytometry panel. The hierarchical gating strategy is shown in **Fig. 1B.** Viable cells were initially identified as parent gates for CD45+, followed by CD3+, and finally CD4+, and CD8+. Tissue-resident memory (T_{RM}) cells were subsequently defined by the co-expression of CD103 and CD69 on both CD8+ and CD4+ T cells, or by CD69 expression alone on CD4+ T cells (**Fig. 1B**).

We observed no significant differences in the abundance of nasal cells expressing canonical markers; CD45, CD3, and CD4, although CD8+ T cell counts showed an increase at 4 weeks (p= 0.1405) and 12 weeks (p=0.2120) following first vaccination (**Fig. 2A**). Although not statistically significant, CD45+ and CD4+ nasal cell frequencies showed a reduced trend (p=0.3693 and 0.6003 respectively) at week 12 (V02) compared to baseline while a significant increase was observed in the proportion of CD8+ T cells in the nasal cavity (*p=0.0500) (**Fig. 2B**). In peripheral blood, the proportion of CD8+ T cells increased significantly at week 12 compared to baseline (*p = 0.0484) while the CD3+ and CD4+ T cell frequencies remained unchanged following vaccination (**Fig.2C**).

Phenotypically, we observed a trend towards decreased CD4+ T_{RM} (CD103+CD69+); p=0.1579 and increased CD8+ T_{RM} (CD103+CD69+) cell counts (p = 0.2469) at week 12 compared to baseline (**Fig. 3A**). However, there was a significant decrease in CD4+ non-T_{RM} cells expressing CD103+ (p = 0.02), while a trend towards increased CD8+ non-T_{RM} cells was observed at week 12 (p=0.1901 and p=0.2123) **(Fig. 3B)**. Interestingly, the frequency of CD8+ T cells co-expressing CD69 and CD103 significantly declined in blood (*p=0.03) (**Fig. 3C**), and no significant differences were observed in non-T_{RM} proportions in blood following vaccination (**Fig. 3D**).

We next compared immune responses among recipients of different vaccine platforms. At week 4 post-vaccination, participants who had received the J&J vaccine had significantly higher nasal immune cell abundances (CD45+, CD3+, CD4+, and CD8+) compared to those who received the Pfizer vaccine (*p=0.018, 0.0136, 0.0091, and 0.0182, respectively) (**Fig. 4A**). However, at week 12, a non-significant trend towards reduced immune cell abundances was observed among J&J recipients compared to Pfizer recipients, likely associated with the Pfizer booster dose at week 4 (**Fig. 4A**). Similar trends were observed in nasal T_{RM} cells with J&J recipients having significantly higher CD4+ CD69+ T_{RM} cell counts than Pfizer recipients at week 4 (*p=0.0182). While this trend was reversed in week 12, the change was not statistically significant (**Fig. 4B).**

Functionally, nasal CD8+ SARS-CoV-2-specific (IFN-γ, perforin, and TNF) responses showed increasing trends among Pfizer vaccine recipients (p=0.3879, 0.7394 and 0.1818 respectively) compared to J&J at week 4 post-vaccination except for CD107a (p=0.4591). On the other hand, week 12 had the trend reversed with J&J showing higher trends over Pfizer group; CD107a (p= 0.5714), IFN-γ (p= 0.4464), perforin (p= 0.7857), and TNF (p= 0.5536) (**Fig. 5**).

SARS-CoV-2 specific CD8+ T-cell responses in blood revealed no significant differences between Pfizer and J&J recipients at week 4, although CD8+IFNγ+ responses were more elevated (p=0.0909) among J&J recipients compared to Pfizer. Meanwhile CD8+perforin+ and CD107a+ expression were similar (p=0.8848 and 0.7758 respectively) in the two vaccine groups at week 4 (**Fig. 6**). By contrast, at week 12, J&J vaccine recipients exhibited significantly higher SARS-CoV-2–specific CD8+ T cell frequencies of CD8+ CD107a+ (*p < 0.05) and CD8+ IFN-γ+ (*p < 0.05) compared to Pfizer. However, perforin-expressing CD8+ T-cell responses did not differ significantly between the two vaccine groups at this timepoint (**Fig. 6**).

Discussion

The COVID-19 pandemic led to a global push for vaccine development and deployment (38). Although vaccination effectively reduced severe disease and mortality through robust systemic and localized mucosal immune responses, vaccine responses in the upper respiratory tract (URT) of individuals living in low- and middle-income countries remain largely understudied. In this study, we investigated immune cell profiles following Pfizer–BioNTech (mRNA) and Johnson & Johnson (J&J; viral vector) COVID-19 vaccination in the URT, the primary site of viral entry and replication among Ugandan participants. Most of our study participants received the Pfizer vaccine, as at the time it was one of the few vaccines approved for use in Uganda and was readily available at health facilities. Although the J&J vaccine had also received approval, its distribution was more logistically challenging compared to Pfizer, resulting in limited availability in government health facilities and consequently fewer doses were taken up.

Following vaccination, we observed a trend towards increased CD8+ T cell abundance in the nasal cavity followed by significant increases in frequencies in URT and peripheral blood at week 12. These findings are consistent with previous studies that showed that both mRNA and viral vector vaccines effectively elicit mucosal and systemic CD8+ T-cell responses which are crucial for clearing virally infected cells and are key to protective immunity against SARS-CoV-2 (28, 39-41). On the other hand, we also observed a trend towards reduced CD4+ T cell abundance and frequencies in the nasal cavity and blood at week 12 which may suggest that their functional role as helper T cells could be rapidly executed without a sustained increase in their numerical frequency.

Tissue-resident memory (T_{RM}) T cells, residing in tissues like the URT, are crucial for providing rapid, localized protection against reinfection (42, 43). Our study profiled T_{RM} cells by the co-expression of CD103 and CD69 on CD4+ and CD8+ T cells, or by CD69 expression alone on CD4+ T cells, showing a trend towards a decreased proportion of CD4+ T_{RM} cells but an increased trend in CD8+ T_{RM} cells in the nasal cavity at week 12, suggesting that vaccination may differentially influence the establishment or maintenance of these two T_{RM} cell subsets. The observed decline in nasal CD4+ non-T_{RM} cells expressing CD103 at week 12 is interesting and might represent a specific lineage with a distinct functional fate or migration of this cell subset elsewhere warranting further investigation in larger studies.

Conversely, the increasing trend in nasal CD8+ T_{RM} cells aligns with the understanding that robust, localized CD8+ T_{RM} populations contribute toward early viral control at the site of entry (44). Interestingly, we observed a significant decline in the frequency of CD8+ T cells co-expressing CD69 and CD103 in blood which is similar to an earlier observation made by our group (28) and is not surprising as by definition, T_{RM} cells are tissue-resident and are not typically in high abundance in peripheral circulation (45) however, this finding could further be explored in future immunogenicity studies. These data underscore the importance of sampling mucosal sites to accurately assess the T_{RM} cell responses to vaccination.

A key finding of our study was the significant difference in URT immune cell abundances between recipients of the Pfizer–BioNTech mRNA and J&J viral vector vaccine. At week 4 post-vaccination, the single-dose J&J vaccine recipients demonstrated significantly higher counts of nasal immune cells and CD4+ CD69+ T_{RM} cells compared to those in the Pfizer-BioNTech group. However, it is important to acknowledge that other researchers have indicated that mRNA vaccines may elicit equal or higher for certain T-cell responses (46, 47). Nevertheless, at week 12, this trend was reversed, with Pfizer recipients showing a non-significant trend towards higher immune cell abundances.This early robust response in J&J recipients might be attributed to viral vector platform, which have previously shown better efficiency in stimulating a potent innate and early adaptive immune responses at the mucosal sites (48) compared to the lipid nanoparticle delivery system in the Pfizer-BioNTech mRNA vaccine. Furthermore, the observed increase in immune cell abundance at week 12 among Pfizer-BioNTech recipients could be explained by the booster dose given at week 4. This additional stimuli is known to significantly enhance both the cellular and humoral immune responses, aligning with previous studies that demonstrate the superior effectiveness and longevity of multi-dose mRNA vaccine regimens (49-51).

With respect to URT immune cell functionality, we observed higher CD8+ antigen-specific responses (IFN-γ, perforin, and TNF) at week 4 among Pfizer recipients, with the pattern reversing by week 12. Additionally, J&J recipients showed significantly higher peripheral blood CD8+ T cells expressing CD107a+ and IFN-γ+ at week 12 compared to Pfizer. These findings further demonstrate the ability of both the mRNA and viral vectored vaccine to induce immune responses with specific differences in the timing and compartmentalization of T cell responses. Such distinctions are important, as both mucosal and peripheral immunity contribute differently to protection against infection and disease.

Our study's major limitation was the small sample size, which was further impacted by limited follow-up at subsequent visits, reducing the number of participants available for longitudinal analysis. This made it difficult to draw robust conclusions about long-term trends. A larger, more diverse cohort with a higher retention rate would be necessary to confirm our findings and generalize them to a broader population. Our data are also limited by the fact that we were unable to explore environmental exposures/infections including prior natural SARS-CoV-2 infection, pre-existing disease like asthma, allergies and common colds that could influence mucosal responses to these vaccines. Future vaccine studies should investigate the effect of such factors on mucosal responses to vaccines. Additionally, the observed differences between vaccine platforms, while interesting, should be interpreted with caution given the small number of participants particularly in the J&J group making the direct comparison challenging. A randomized controlled trial design would be needed to truly compare the immune responses induced by different vaccine platforms.

Despite its limitations, our study offers valuable insights into the dynamic cellular immune responses in the URT of Ugandans after COVID-19 vaccination. We highlight the distinct effects of different vaccine platforms and underscore the importance of booster doses. Our findings serve as a foundation for future, larger-scale studies to unravel the complex mechanisms of mucosal immunity against respiratory viruses.

Declarations

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Data availability statement

The dataset related to this study is available on request from the corresponding author.

Disclosures

We acknowledge the use of Gemini 3 Pro generative AI solely to improve language fluency and correct grammatical errors. The AI was not used to generate scientific content.

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Figures

Fig. 1A

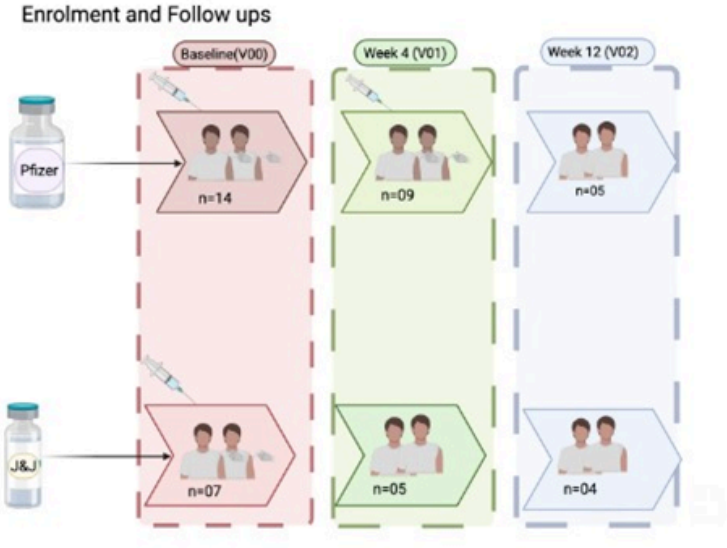


Fig. 1B

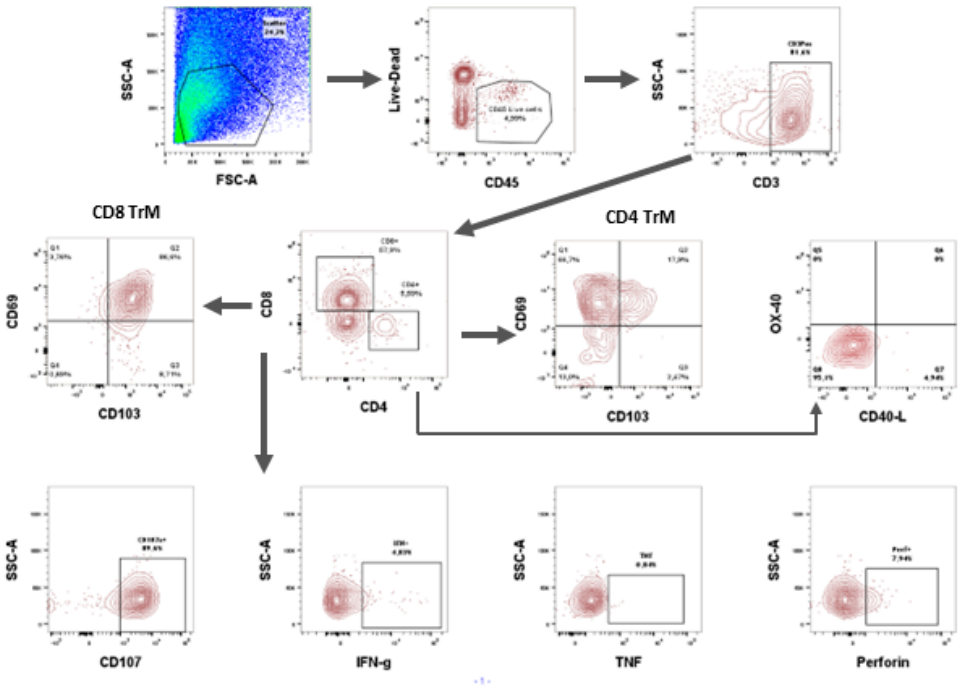


Figure 1

(A) Enrollment and follow-up of study participants receiving either the Pfizer or J&J vaccine at Baseline/enrollment (V00), Follow-up visit at Week 4 (V01) and at Week 12 (V02) post vaccination. **(B)** Representative flow cytometry plots showing gating strategy used to define lymphocytes, nasal CD45+ immune cells, CD3+, CD4+ and CD8+ T cells. CD4+ and CD8+ T cells that were T_{RM}, and antigen specific

T cells defined by expression of OX-40 and CD40L for CD4+ T cells and CD107a, IFN-γ, Perforin and TNF for CD8+ T cells.

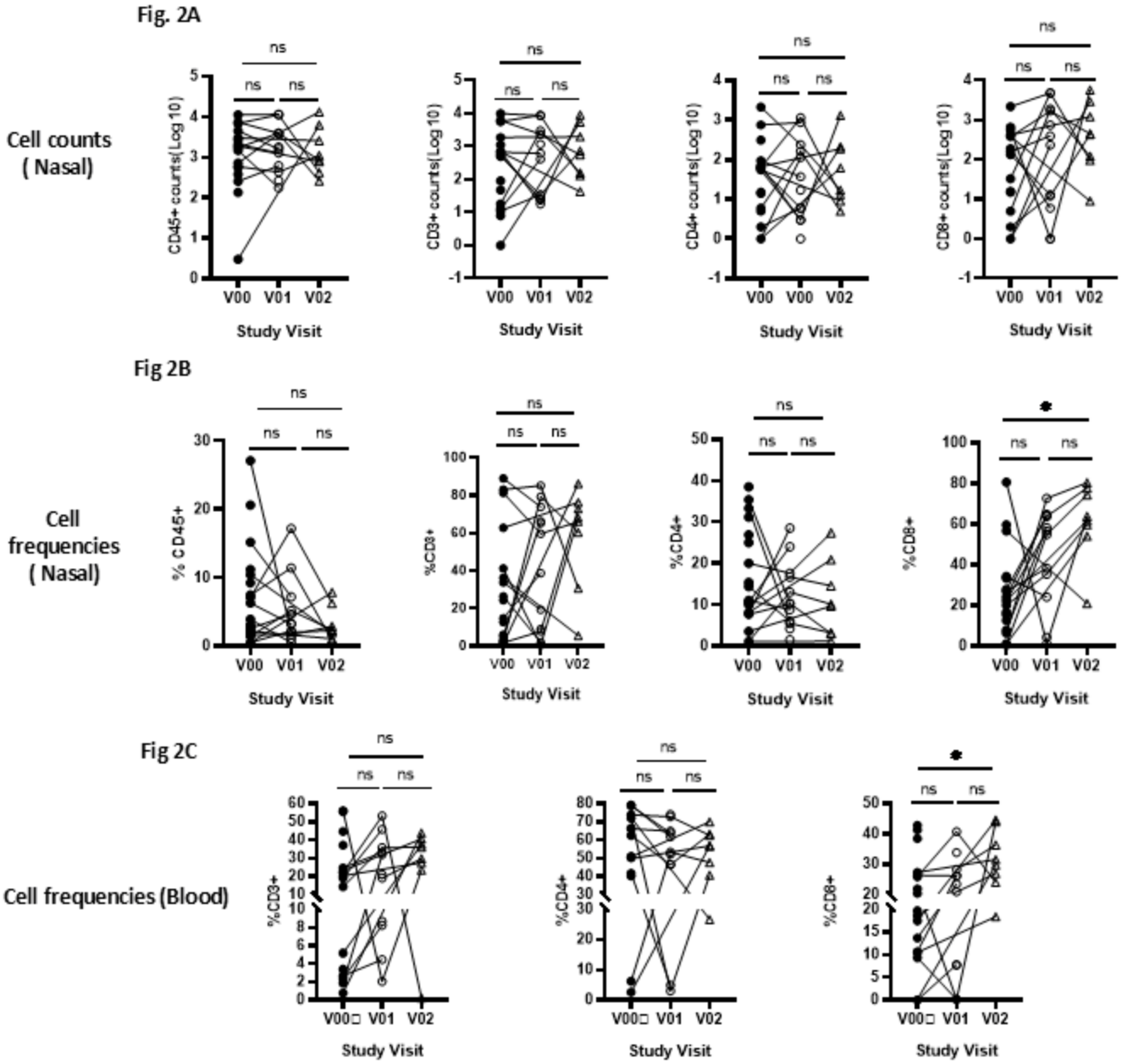


Figure 2

Nasal cell counts, frequencies and peripheral blood T cell populations post vaccination (A) No changes in nasal CD45+, CD3+ and CD4+ T cells, while an increasing trend in CD8+ T cel counts (ns). **(B)** A higher expression %CD8+ nasal T cells at week 12 (*$p=0.0500$) and no changes in nasal CD45+, CD3+, CD4+ T cell frequencies (ns). **(C)**Elevated CD8+ T cell frequencies in blood at week 12 (*$p=0.0484$) but no changes in %CD3+ and CD4+ T cell (ns). * Significant, ns - non-significant. Paired, nonparametric Linear mixed models were used to estimate *p values*. * Significant, ns - non-significant.

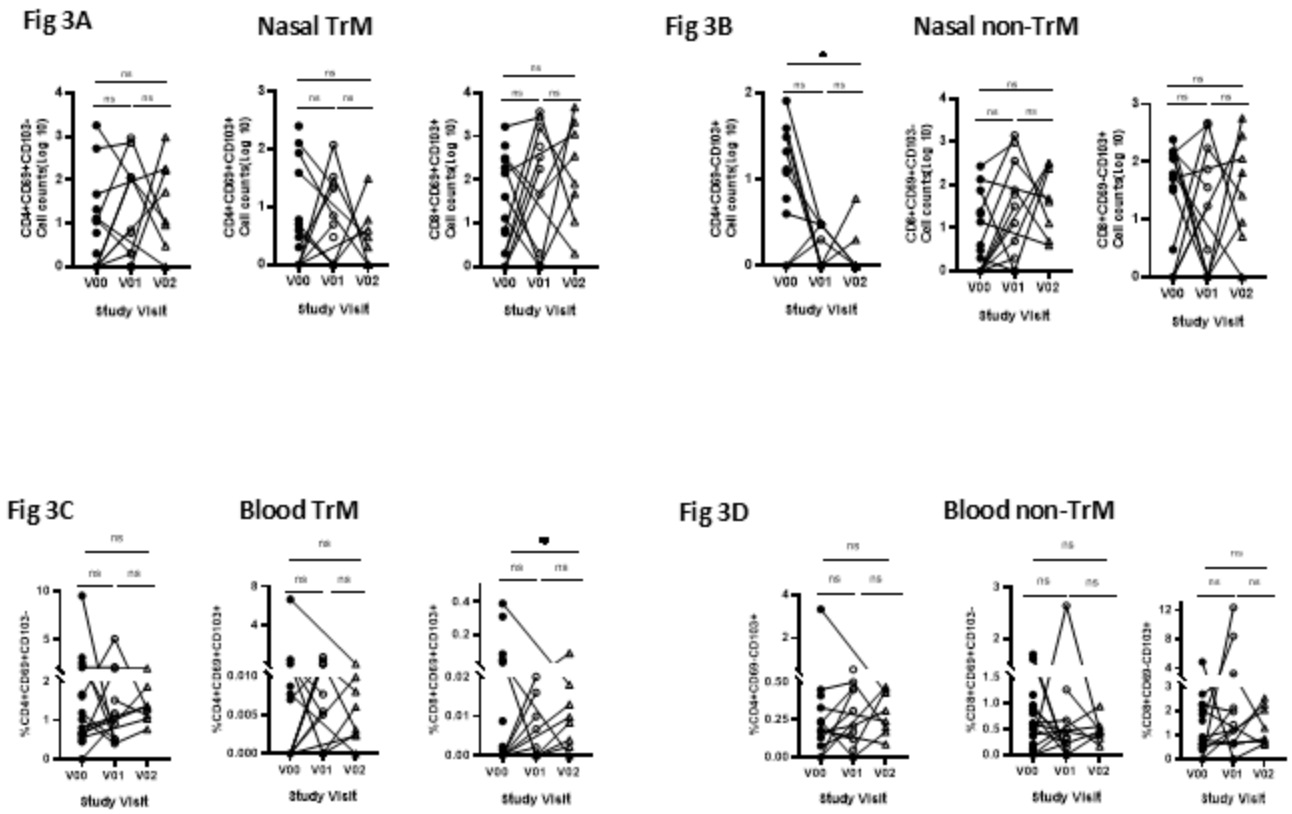


Figure 3

Nasal (A) T_{RM} and (B) Non T_{RM} nasal cell counts and peripheral blood T cell frequencies post vaccination. (A) No changes in nasal CD4+ T_{RM} cells while a trend towards increased CD8+ T_{RM} cell (ns). (**B)** Decline in nasal CD4+ non T_{RM} cells at week 12; CD4+CD69-CD103+ **p=0.0246* while no change in CD8+ non TRM cells (ns). **(C)** No change in peripheral blood CD4+ T_{RM} cell subsets while CD8+CD69+CD103+ cells declined at week 12, (**p=0.0300)*. (**D)** Peripheral blood CD4+ and CD8+ non T_{RM} cell subsets (ns). Paired, nonparametric Linear mixed models were used to estimate *p values*. * Significant, ns - non-significant.

Fig. 4A

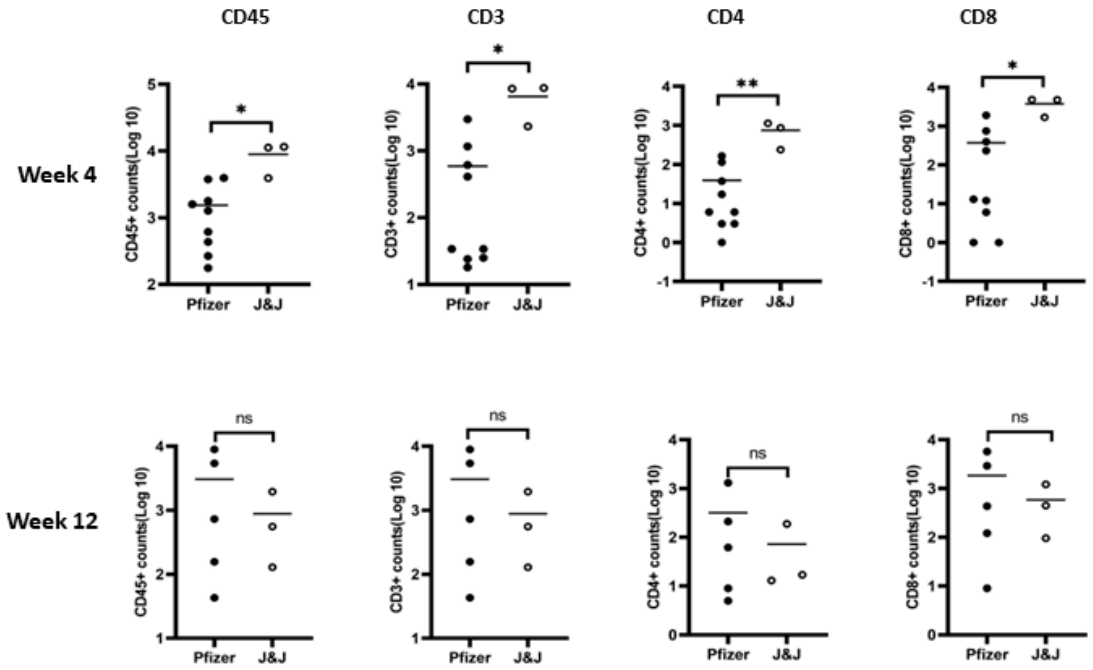


Fig. 4B

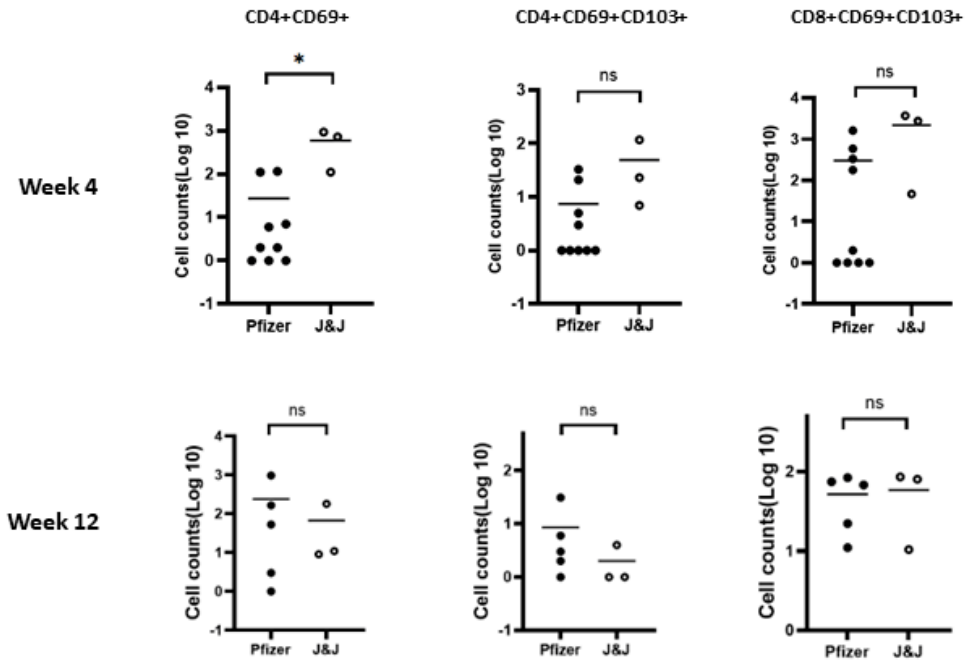


Figure 4

(A) Comparison of T cell responses between Pfizer and J&J vaccine groups at 4 Weeks (V01) Pfizer n=09, J&J n=03 and 12 weeks (V02) Pfizer n=05, J&J n=03. **(B)** Nasal CD4+ and CD8+ T_{RM} cell abundance between Pfizer and J&J recipients at V01 and V02. Non-parametric Mann-Whitney tests were used to estimate *p values*. * Significant, ns - non-significant.

Fig. 5A

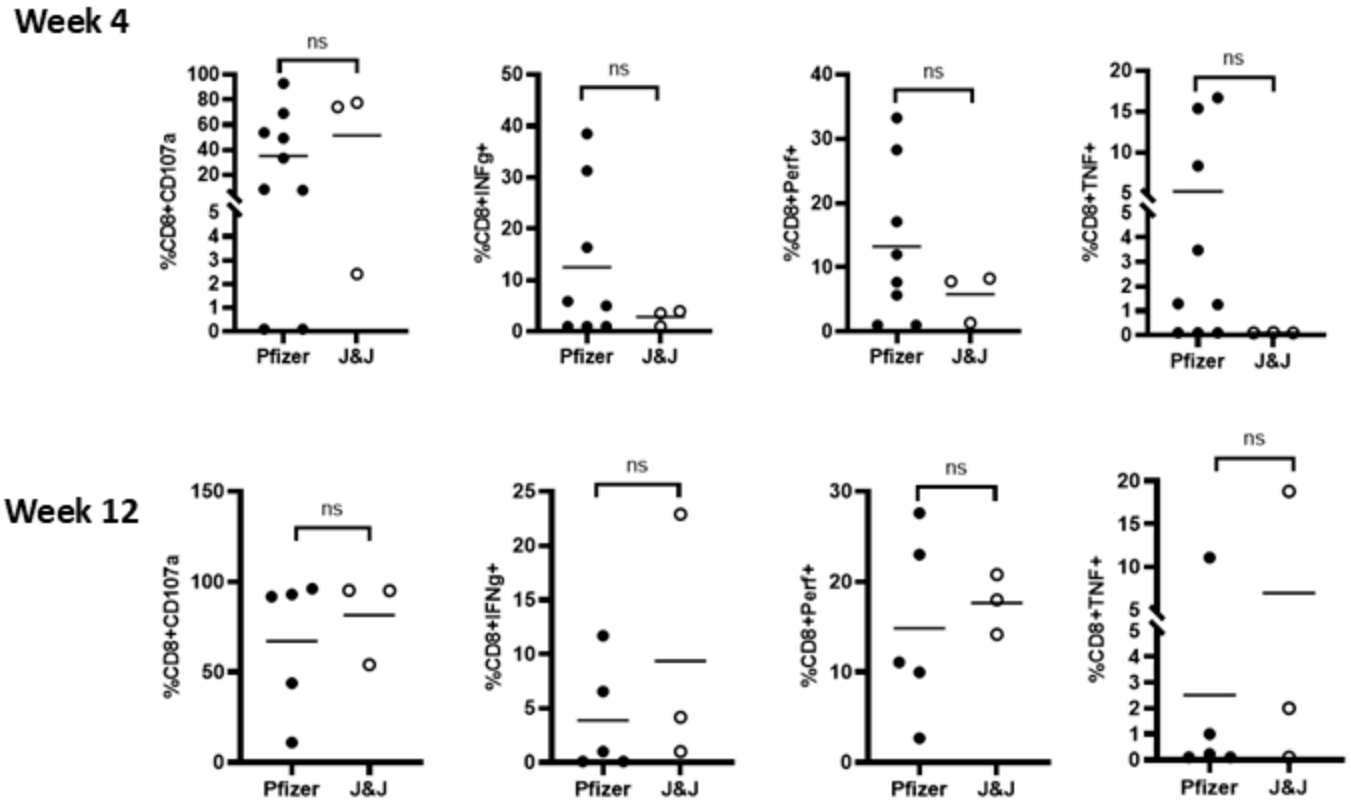


Figure 5

Comparison of nasal SARS CoV 2 antigen specific CD8+ T cell responses between Pfizer and J&J vaccine groups at Week 4 (V01) and week12 (V02) study visits. Non-parametric Mann-Whitney tests were used to estimate *p values*. * Significant, ns - non-significant.

Fig. 6

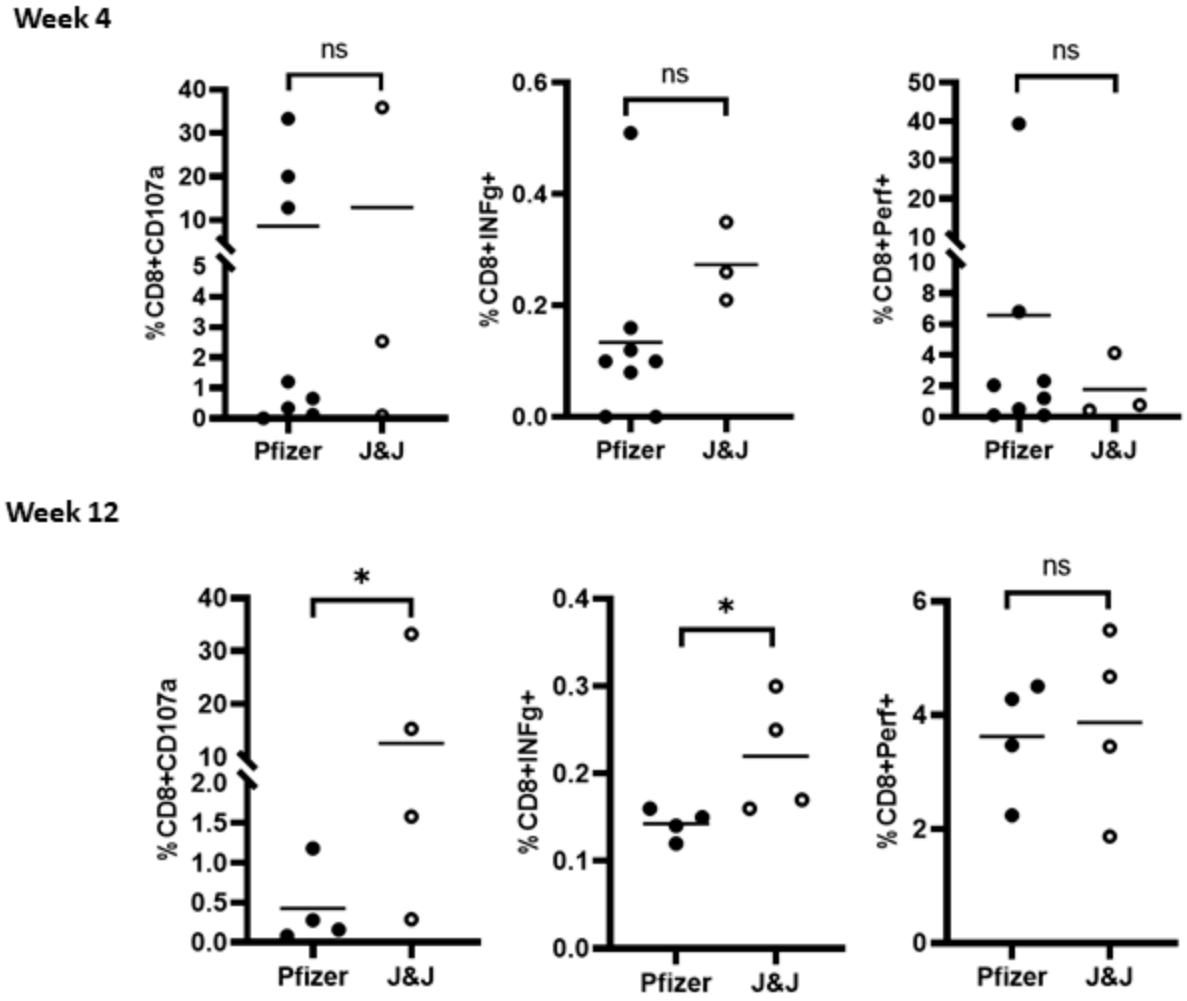


Figure 6

Comparison of SARS-CoV-2 antigen specific CD8+ T cell responses in blood between Pfizer and J&J vaccine groups at Week 4 (V01) and week12 (V02) study visits. Non-parametric Mann-Whitney tests were used to estimate *p values*. *Significant, ns - non-significant.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalTable1VMBiribawaetal.xlsx
- Supplementarytable2VMBiribawaetal.docx