At Least Three Doses of Leading Vaccines Essential for Neutralisation of SARS-CoV-2 Omicron Variant


Acknowledging the Wathaurong Community, Traditional Owners of Greater Geelong

And funding from:

COVID-19
WHO meeting on COVID-19 Vaccines Research

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Honorary Professor, University of York

Acknowledging the Wathaurong Community, Traditional Owners of Greater Geelong

And funding from:
• Doherty Institute
• Dept of Microbiology and Immunology
• Victorian Infectious Diseases Reference Laboratory (VIDRL)

• CSIRO
• Australian Centre for Disease Preparedness (ACDP) PC4/BSL4 Team
• Dr Nagendra Singanallur and Dr StellaMay Gwini (Barwon Health) for study design and biostatistics, and Dr Michael Kuiper (Data61) for biomolecular modelling

• Shruthi, Simran and all collaborators
Omicron vs Delta VOCs

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## Study overview – participants

<table>
<thead>
<tr>
<th></th>
<th>AstraZeneca</th>
<th>Moderna</th>
<th>Pfizer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donors</strong></td>
<td>n=6</td>
<td>n=12</td>
<td>n=15</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>n=3</td>
<td>n=6</td>
<td>n=5</td>
</tr>
<tr>
<td>Female</td>
<td>n=3</td>
<td>n=6</td>
<td>n=10</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median (Range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58 (57-65)</td>
<td>41.5 (29-70)</td>
<td>31 (29-35)</td>
</tr>
<tr>
<td>Female</td>
<td>57 (31-59)</td>
<td>38.5 (27-47)</td>
<td>33.5 (25-57)</td>
</tr>
<tr>
<td><strong>Samples Used</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-bleed (Baseline)</td>
<td>n=6 (3M, 3F)</td>
<td>n=12 (6M, 6F)</td>
<td>n=15 (5M, 10F)</td>
</tr>
<tr>
<td>2 weeks Post-2(^{nd}) Dose</td>
<td>n=6 (3M, 3F)</td>
<td>n=12 (6M, 6F)</td>
<td>n=15 (5M, 10F)</td>
</tr>
<tr>
<td>6 months Post-2(^{nd}) Dose</td>
<td></td>
<td></td>
<td>n=15 (5M, 10F)</td>
</tr>
<tr>
<td>2 weeks Post-3(^{rd}) Dose</td>
<td></td>
<td></td>
<td>n=6 (3M, 3F)</td>
</tr>
</tbody>
</table>
Study overview – fold changes

<table>
<thead>
<tr>
<th>VIC31 Titre Comparison</th>
<th>AstraZeneca</th>
<th>Moderna</th>
<th>Pfizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>7.0-fold higher</td>
<td>7.2-fold higher</td>
<td></td>
</tr>
<tr>
<td>Moderna</td>
<td>7.0-fold lower</td>
<td></td>
<td>1.0-fold higher</td>
</tr>
<tr>
<td>Pfizer</td>
<td>7.2-fold lower</td>
<td>1.0-fold lower</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pfizer Timepoint Comparison (VIC31)</th>
<th>6mo Post-2(^{nd}) Dose</th>
<th>2w Post-3(^{rd}) Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks Post-2(^{nd}) Dose</td>
<td>8.2-fold lower</td>
<td>3.2-fold higher</td>
</tr>
<tr>
<td>6 months Post-2(^{nd}) Dose</td>
<td>25.9-fold higher</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pfizer Timepoint Comparison (Delta)</th>
<th>6mo Post-2(^{nd}) Dose</th>
<th>2w Post-3(^{rd}) Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks Post-2(^{nd}) Dose</td>
<td>8.3-fold lower</td>
<td>4.5-fold higher</td>
</tr>
<tr>
<td>6 months Post-2(^{nd}) Dose</td>
<td>37.5-fold higher</td>
<td></td>
</tr>
</tbody>
</table>

Explore role of T cell immunity (in progress)
Study overview – statistics

• All analysis performed using R (R Core Team, 2019)

• Variables were declared as follows:
  • Vaccines (Pfizer; Moderna; AstraZeneca)
  • Gender (Male; Female)
  • Age (<35 – Young; 35-60 – Middle; >60 – Senior)
  • Day post-vaccination (Baseline – 0 dpv; 2 weeks post 2\textsuperscript{nd} dose; 6 months post 2\textsuperscript{nd} dose; and with Pfizer alone 2 weeks post 3\textsuperscript{rd} dose)
  • Variant (VIC31; Delta; Omicron BA.1.1)

• One way ANOVA performed to compare different variables: vaccines, gender, age, and variants. Post hoc done using Bonferroni correction to obtain adjusted ‘p-values’ for significant groups.

• Two way ANOVA performed to compare interactions between variables. Post hoc done using Tukey’s HSD to obtain adjusted ‘p values’ for significant groups.

• Linear mixed models with effects were constructed in R using ‘lme’ library with forward selection of modes using lowest AIC values. AIC=Akaike Information Criterion.

• Codes for statistical significance: <0.001 ‘****’; 0.01 ‘**’; 0.05 ‘*’; 0.1 ‘.’; ‘NS’ >0.05
Comparison of VNT titres in human subjects

H  VNT with two dose of AstraZeneca vaccine

variant
Delta
Omicron
VIC31

G  VNT with two dose of Moderna vaccine

F  VNT titres with three doses of Pfizer vaccine

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Comparison of VNT titres in human subjects

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Comparison of VNT titres by gender - Pfizer

L  VIC31 titres
Anova, p = 1.2e-15  Anova, p = 4.2e-09

M  Delta titres
Anova, p = 1.5e-13  Anova, p = 1.5e-07

N  Omicron titres
Anova, p = 2.2e-08  Anova, p = 2e-08

day
1st-0day
2nd-2wk
2nd-6mo
3rd-2wk
Comparison of VNT titres by gender - Moderna

**VIC31 titres**
- Anova, $p = 9.1\cdot10^{-7}$
- Anova, $p = 2.2\cdot10^{-6}$

**Delta titres**
- Anova, $p = 3.2\cdot10^{-7}$
- Anova, $p = 4\cdot10^{-4}$

**Omicron**
- Anova, $p = 0.34$
- Anova, $p = 0.16$

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Comparison of VNT titres by gender - AstraZeneca

R  VIC31 titres  

S  Delta titres  

T  Omicron titres

Anova, p < 2.2e-16  Anova, p = 0.0096

Anova, p = 0.37

Anova, p = 0.37

Anova, p = 0.37

day  

1st-0day  

2nd-2wk  

2nd-6mo  

3rd-2wk

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Comparison of VNT titres by age - Pfizer

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Comparison of VNT titres by age - Moderna

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Comparison of VNT titres by age - AstraZeneca

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Implications for vaccine equity

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Implications for vaccine equity
Warm vaccines

COVID-19 Vector, mRNA and Inactivated vaccines storage temperature requirements

-90 °C
-60 °C
-20 °C
0 °C  2 °C  8 °C
37 °C

Viral Vector vaccines (AZ, Jannsen, Sputnik, CanSino), 2-8 °C, until expiry which varies from 6 months to 12 months.

mRNA Pfizer -90° to -60°C for 6 months
mRNA Moderna -50° to -15°C for 6 months

mRNA Pfizer, 2° to 8°C for 10 weeks
mRNA Moderna, 2° to 8°C for 30 days prior to first use

Inactivated vaccines (Sinopharm, Sinovax and Covaxin), 2° to 8°C

Myrnax Warm Vaccine, up to 4 weeks at 37 °C, up to 90 minutes at 100 °C
Warm vaccines

Immunogenicity and Protective Efficacy of a Highly Thermotolerant, Trimeric SARS-CoV-2 Receptor Binding Domain Derivative


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Labs rush to study coronavirus in transgenic animals – some are in short supply

The first results are emerging: teams in China have reported initial findings from infecting monkeys and mice that have the human ACE2 gene. Labs working on ferrets say they should also have initial results soon: a team led by virologist S. S. Vasan at the Australian Animal Health Laboratory in Geelong has found that the animals are susceptible to SARS-CoV-2. The researchers are now studying the course of infection, before testing potential vaccines. Ferrets are a popular model for influenza and other respiratory infections because their lung physiology is similar to that of humans, and researchers hope they will mimic aspects of COVID-19 in people, such as its spread.

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ChAdOx1 nCoV-19 (AZD1222) vaccine candidate significantly reduces SARS-CoV-2 shedding in ferrets

Intranasal route

Treatment Groups
- Control (n=6)
- Prime-Only Intramuscular (n=8)
- Prime-Only Intranasal (n=8)
- Prime-Boost Intramuscular (n=7)
- Prime-Boost Intranasal (n=8)