COVID-19 research: SARS-CoV-2 variants

Achievements, lessons learned and next steps
Understanding the phenotypes of the successive variants of SARS-CoV-2

A huge amount of viral sequencing data has been generated during this COVID pandemic.

Some virus variants have emerged with phenotypes that have enabled them to spread across the world.

To help what to expect in the future we need to understand what underlies the phenotypes of the successful variants.
Successive variants of SARS-C0V-2

- Wuhan like virus
- D614G
- Alpha
- Delta
- Beta/Gamma
- Local circulation
- Omicron

United Kingdom
Early variants had increased transmissibility

- Higher or longer virus shedding
- Different disease or tropism
- More efficient entry (lower human infectious dose)
- Evasion of innate immune response
- Evasion of acquired immune response
Genetic determinants of increased transmissibility

- Increased exposure of receptor binding domain:
  Spike D614G

- Increased affinity for ACE2:
  Spike N501Y
Mutations in variants outside Spike gene also impact the virus

Mutations in N gene that affect innate immune control and virion assembly have arisen

We understand very little of the impact of mutations that have arisen elsewhere in the genome
Omicron carries an unprecedented number of mutations in Spike

This raises concerns for the effectiveness of vaccines that use Spike based on the first wave virus
Omicron is less well neutralized by antibodies raised to the vaccine

Antibody titres are restored after a 3rd dose boost
Vaccine remains effective against severe disease

Table 2. Hazard ratios and vaccine effectiveness against hospitalisation (all vaccine brands combined). OR = odds ratio, HR = hazards ratio, VE = vaccine effectiveness

<table>
<thead>
<tr>
<th>Dose</th>
<th>Interval after dose (weeks)</th>
<th>OR v symptomatic disease</th>
<th>HR vs hospitalisation</th>
<th>VE vs hospitalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4+</td>
<td>0.74 (0.72-0.76)</td>
<td>0.57 (0.38-0.85)</td>
<td>58% (37-72)</td>
</tr>
<tr>
<td>2</td>
<td>2 to 24</td>
<td>0.81 (0.8-0.82)</td>
<td>0.45 (0.36-0.56)</td>
<td>64% (54-71)</td>
</tr>
<tr>
<td>2</td>
<td>25+</td>
<td>0.94 (0.92-0.95)</td>
<td>0.6 (0.49-0.74)</td>
<td>44% (30-54)</td>
</tr>
<tr>
<td>3</td>
<td>2 to 4</td>
<td>0.32 (0.31-0.33)</td>
<td>0.26 (0.19-0.35)</td>
<td>92% (89-94)</td>
</tr>
<tr>
<td>3</td>
<td>5 to 9</td>
<td>0.42 (0.41-0.43)</td>
<td>0.29 (0.23-0.37)</td>
<td>88% (84-91)</td>
</tr>
<tr>
<td>3</td>
<td>10+</td>
<td>0.5 (0.49-0.51)</td>
<td>0.34 (0.26-0.44)</td>
<td>83% (78-87)</td>
</tr>
</tbody>
</table>

Bailey et al. Pirbright Institute, with UK-HSA consensus study
Omicron infection is associated with milder disease

SARS-CoV-2 variants of concern and variants under investigation in England: Technical briefing 36

Table 3. Odds of ICU-HDU admission among hospitalised Omicron cases versus Delta cases, acute NHS trusts, England

|                     | Number admitted to ICU/HDU | Total hospitalisations | Unadjusted OR | 95% CI | P>|z| | Adjusted OR* | 95% CI | P>|z| |
|---------------------|-----------------------------|------------------------|---------------|--------|-----|----------------|--------|-----|-----|
| Delta*              | 31                          | 361                    | 1.00          |        |     | 1.00          |        |     |     |
| Omicron*            | 13                          | 439                    | 0.32          | 0.17   | 0.63| 0.001         | 0.51   | 0.22| 1.15| 0.103|

* sequenced linked cases/SQTF status if sequence data not available
* adjusting for: age (<40y, 40 to 49, 50 to 64, ≥65y), sex, vaccination status on admission (unvaccinated, D1 only, 2 Doses only, 3D+1), levels of comorbidity (1, 2 or ≥3 conditions), ethnicity and hospital random effects

Halfmann et al Nature 2022

Omicron
D614G
Research gaps: questions for the future

- Are antigenic distance and milder disease separable phenotypes?

- How will heterogeneous immunity across the world impact future evolution?

- Will future variants co-circulate, will they recombine?

- Will the virus reside in animal reservoirs?

- How will we track the growth of the next variants if there is less testing and sequencing?
Lessons learned

Rapid responses to emerging variants can be strengthened by working together in consortia.

Collaborations between academics and government institutes can enable a strong interdisciplinary approach.