Immune Response to SARS-CoV-2 Omicron Breakthrough is a Recall of Vaccine-Induced Memory

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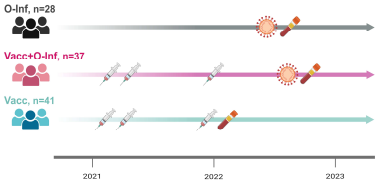
BACKGROUND

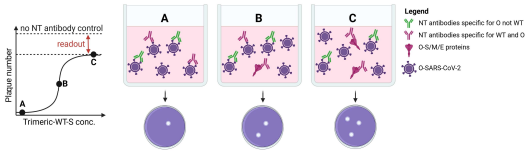
- About 65% of the global population completed the primary SARS-CoV-2 vaccination protocol.
- 35 additional doses were administered per 100 people.
- The emergence of the highly mutated omicron variant led to soaring numbers of breakthrough infections.
- **Does SARS-CoV-2 immunity adapt by generation of *de novo* response to mutated epitopes or remains imprinted by the wild-type based vaccine?**
- If SARS-CoV-2 mutates to the point where it is not efficiently neutralized by the vaccine-induced immunity this could lead to the development of original antigenic sin.

METHODS

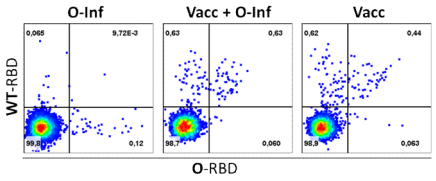


- Immune response specific for the **mutated regions** of the omicron SARS-CoV-2 surface proteins.

- **Antibodies:** competitive ELISA, competitive NT assay



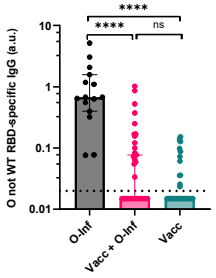
- **B cells:** flow cytometry
- **T cells:** flow cytometry

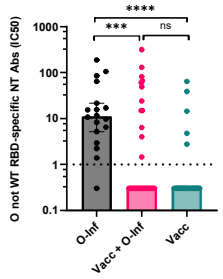


Previous vaccination inhibits the formation of response to mutated regions of omicron spike protein, a precondition for the original antigenic sin.

RESULTS

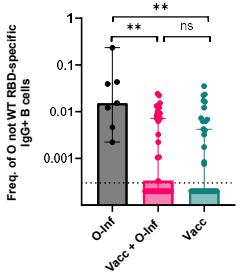
- Omicron breakthrough infection does not significantly increase the levels of **neutralizing antibodies specific for mutated regions of omicron surface proteins.**

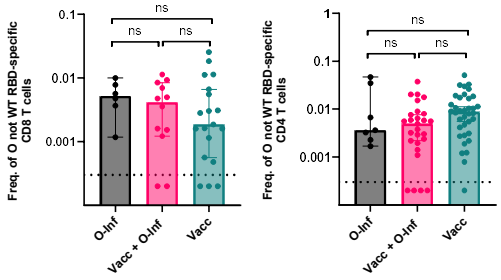




- Omicron breakthrough infection does not significantly increase the levels of **IgG specific for mutated regions of RBD.**

- Previous vaccination inhibits the formation of **IgG+ B cells specific for mutated regions of omicron RBD** following breakthrough infection.





- The magnitude **of T cell response to mutated regions of the omicron spike protein** is comparable between the vaccinated individuals with or without omicron breakthrough and unvaccinated omicron-infected individuals.

CONCLUSIONS

- **Vaccination imprints the B cell response** to omicron SARS-CoV-2 breakthrough infection and hinders the production of antibodies and memory B cells specific for the mutated epitopes of the omicron surface proteins.
- T-cell response to mutated epitopes of the omicron spike protein is present.
- Likely due to the **high cross-reactivity of T cells** rather than the formation of *de novo* response further supporting imprinting of the adaptive immunity.

SIGNIFICANCE

- **The imprinting of SARS-CoV-2 immunity by vaccination could lead to the development of original antigenic sin if future variants overcome the vaccine-induced immunity.**
- As this would inhibit the formation of adaptive immune response, infections with escape variants could become life-threatening.
- Our findings call for the development of variant-adapted vaccines that would not only boost the response to conserved regions of the spike protein but also evoke a *de novo* response targeting mutated epitopes.

ACKNOWLEDGEMENTS

- The study was supported financially by the State of North Rhine-Westphalia, and the Viral NRW Network (grant number: CPS-1-1C).
- We thank the participants of this study who generously provided their samples.

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DZIF Deutsches Zentrum für Infektionsforschung

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