Immune responses and immune memory to SARS-CoV-2 and COVID-19 vaccination: lessons for future vaccines

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FOR IMMUNOLOGY

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COVID-19 has killed more Americans than all the wars of the 20\textsuperscript{th} century combined
Do people develop immune memory to COVID-19?

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INTRODUCTION: Immunological memory is the basis for durable protective immunity after infections or vaccinations. Duration of immunological memory after severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and COVID-19 is unclear. Immunological memory can consist of memory B cells, antibodies, memory CD4+ T cells, and/or memory CD8+ T cells. Knowledge of the kinetics and interrelationships among these four types of memory in humans is limited. Understanding immune memory to SARS-CoV-2 has implications for understanding protective immunity against COVID-19 and assessing the likely future course of the COVID-19 pandemic.

RATIONALE: Assessing virus-specific immune memory over at least a 6-month period is likely necessary to ascertain the durability of immune memory to SARS-CoV-2. Given the evidence that antibodies, CD4+ T cells, and CD8+ T cells can all participate in protective immunity to SARS-CoV-2, we measured antigen-specific antibody, memory B cells, CD4+ T cells, and CD8+ T cells in the blood from subjects who recovered from COVID-19, up to 8 months after infection.

RESULTS: The study involved 254 samples from 188 subjects of 254 samples, including 64 samples from 60 to 8 months after infection. Fifty-one subjects in the study provided longitudinal blood samples, allowing for both cross-sectional and longitudinal analyses of SARS-CoV-2-specific immune memory. Antibodies against SARS-CoV-2 spike and receptor binding domain (RBD) declined moderately over 8 months, comparable to several other reports. Memory B cells against SARS-CoV-2 spike actually increased between 1 month and 8 months after infection. Memory CD8+ T cells and memory CD4+ T cells declined with an initial half-life of 3 to 5 months. This is the largest antigen-specific study to date of the four major types of immune memory for any viral infection.

Among the antibody responses, spike immunoglobulin G (IgG), RBD IgG, and neutralizing antibody titers exhibited similar kinetics. Spike IgG was still present in the large majority of subjects at 6 to 8 months after infection. Among the memory B cell responses, IgM was the dominant isoform, with a minor population of IgG memory B cells. IgM memory B cells appeared to be short-lived. CD8+ T cells and CD4+ T cell memory was measured for all SARS-CoV-2 proteins. Although ~70% of individuals possessed detectable CD8+ T cell memory at 1 month after infection, that proportion declined to ~50% by 6 to 8 months after infection. For CD4+ T cell memory, 98% of subjects had detectable SARS-CoV-2 memory at 1 month after infection, and the proportion of subjects positive for CD4+ T cells (39%) remained high at 6 to 8 months after infection. SARS-CoV-2 spike-specific memory CD4+ T cells and receptor binding domain (RBD) declined moderately over 8 months, comparable to several other reports. Memory B cells against SARS-CoV-2 spike actually increased between 1 month and 8 months after infection. Memory CD8+ T cells and memory CD4+ T cells declined with an initial half-life of 3 to 5 months. This is the largest antigen-specific study to date of the four major types of immune memory for any viral infection.

CONCLUSION: Substantial immune memory is generated after COVID-19, involving all four major types of immune memory. About 95% of subjects retained immune memory at ~6 months after infection. Circulating antibody titers were not predictive of T cell memory. Thus, simple serological tests for SARS-CoV-2 antibodies do not reflect the fidelity and durability of immune memory to SARS-CoV-2. This work expands our understanding of immune memory in humans. These results have implications for protective immunity against SARS-CoV-2 and recurrent COVID-19.

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READ THE FULL ARTICLE AT
https://doi.org/10.1126/science.abd4653
How long does immunological memory to SARS-CoV-2 last?

- **PSV Neutralizing Titer**
  - $t_{1/2} = 125 \text{d}$

- **SARS-CoV-2-specific CD8^+ T cells (%)**
  - $t_{1/2} = 94 \text{d}$
Immune response trajectories in COVID-19

*“Innate” = innate immune response plasma signature

Sette and Crotty, Cell 2021
Layered defenses
Or the swiss cheese model of immunity

Immunological Reviews, 2022
Head-to-head comparison of immune memory to four COVID-19 vaccines

Prof. Daniela Weiskopf
Comparison of immune memory to four COVID-19 vaccines

T1 = baseline
T2 = 14 days
T3 = 35-42 days
T4 = 3 months
T5 = 6 months
Comparison of immune memory to four COVID-19 vaccines

Carolyn Rydzynski Moderbacher, PhD
Jose Mateus, PhD

Cell 2022
Comparison of immune memory to four COVID-19 vaccines

Camila Coelho, PhD
Head-to-head comparison of immune memory to four COVID-19 vaccines
Germinal centers
Lymph node fine needle aspirates (LN FNAs) allow for sampling of the lymph node longitudinally.
Germinal centers can last for > 6 months after an optimized priming immunization.

Dramatically larger and more durable germinal centers than conventional alum-based immunization.

Lee & Sutton et al. Nature 2022
Long-lasting virus-specific germinal centers

Farber and Crotty labs.
Science Immunology 2021
Germinal centers
Hybrid immunity results in potent neutralizing antibody breadth, also with breakthrough infections.
Omicron and memory B cells

SCIENCE IMMUNOLOGY | REPORT

CORONAVIRUS

SARS-CoV-2 Omicron-neutralizing memory B cells are elicited by two doses of BNT162b2 mRNA vaccine

Ryutaro Kotaki t, Yu Adachi t, Saya Moriyama t, Taishi Onodera t, Shoetsu Fukushima, Takaki Nagakura, Keisuke Tonouchi, Kazutaka Terahara, Lin Sun, Tomohiro Takeo, Ayae Nishiyama, Masaharu Shinkai, Kunihiro Oba, Fukumi Nakamura-Uchiyama, Hidefumi Shizumizu, Tadaki Suzuki, Takayuki Matsumura, Masanori Isogawa, Yoshishama Takahashi * t

Increased memory B cell potency and breadth after a SARS-CoV-2 mRNA boost


https://doi.org/10.1038/s41586-022-04778-y

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Open access

A

B

C

D

E

RBD-binding IgG resting B_{L_{pl}} cells

Single-cell sorting

Clonal expansion and IgG secretion

Screening Wuhan RBD-binding clones

NT activity of mAbs in the supernatants

First screening for Wuhan NT

Wuhan PV-NT

% Infection

IC_{50} (ng m^{-1})

Vax 2 Vax 3

Vaccinated

1.3 m 1 m

0.0023 0.60 0.049

290 182 111

0.0001

<0.0003 0.0004

33 3.8 7.1 12.4

0.0001

10^{-1}

10^{-2}

10^{-3}

10^{-4}

WT (R683G)

Delta-RBD (R683G)

Omicron (R683G)

Vax 2 Vax 3

Vax 2 Vax 3

Vax 2 Vax 3

Vax 2 Vax 3

Vax 2 Vax 3

IC_{50} (ng m^{-1})

Vax 2 Vax 3

Vax 2 Vax 3

Vax 2 Vax 3

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Head-to-head comparison of immune memory to four COVID-19 vaccines

Prof. Daniela Weiskopf

Zhang, Mateus, Coelho, Dan, Moderbacher et al. Cell 2022
Layered defenses
Or the swiss cheese model of immunity

Immunological Reviews, 2022
Anatomy of immunity to SARS-CoV-2

It is all a race
A race between the virus and your immune system.
Memory change the race. You then have the headstart instead of the virus.
Layered defenses
Or the swiss cheese model of immunity
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