Understanding T cell immunity to COVID-19 and relationships to vaccine correlates and mechanisms of protection

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WHO Correlates Meeting. Sept 2021

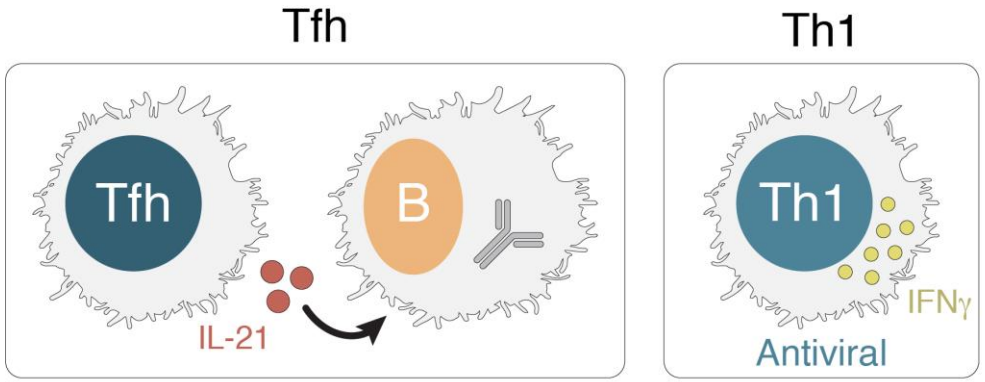
T cells and protective immunity from COVID-19

- The simplest option for any vaccine development is high level, long lasting, neutralizing antibodies.
- Various lines of evidence point to substantial protective contributions of T cells against COVID-19
- It is quite reasonable to consider that hospitalization-level COVID-19 is prevented by any decent combination of antibody, CD4, and CD8 T cells.
- T cells can be measured as potential correlates of immunity, but it has not been done so to date for COVID-19 vaccines

What are mechanisms of protective immunity against COVID-19?

The simplest option for any vaccine development is high level, long lasting, neutralizing antibodies.

- This virus is clearly susceptible to neutralizing antibodies.
- 26 of 28 previous licensed human vaccines have antibodies as the mechanism or correlate of immunity.
- Antibodies are the only mechanism that can provide truly sterilizing immunity.
- Antibodies are a correlate of CD4s: Neutralizing antibody responses almost always depend on CD4 T cell responses. Thus, antibodies are usually a surrogate marker of vaccine-specific CD4 T cells, at least T_{FH} cells.



Adaptive immunity to SARS-CoV-2 and COVID-1
Cell 2021

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- T cell responses correlate with better outcomes and lower viral loads in SARS-CoV-2 infection
- CD8 T cells provide control in monkeys
- Regeneron and Lilly outpatient and inpatient monoclonal antibody clinical trials. Modest impact on viral loads
- Agammaglobulinemic and B cell depleted individuals
  - moderately increased risk of hospitalization with COVID-19
  - COVID-19 in ocrelizumab-treated people with MS is predominantly mild
- 1-dose of Moderna or Pfizer vaccine provided substantial protection in the absence of detectable neutralizing antibodies in most individuals
- Kinetics and tissue distribution of COVID-19

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Anatomy of adaptive immunity to SARS-CoV-2

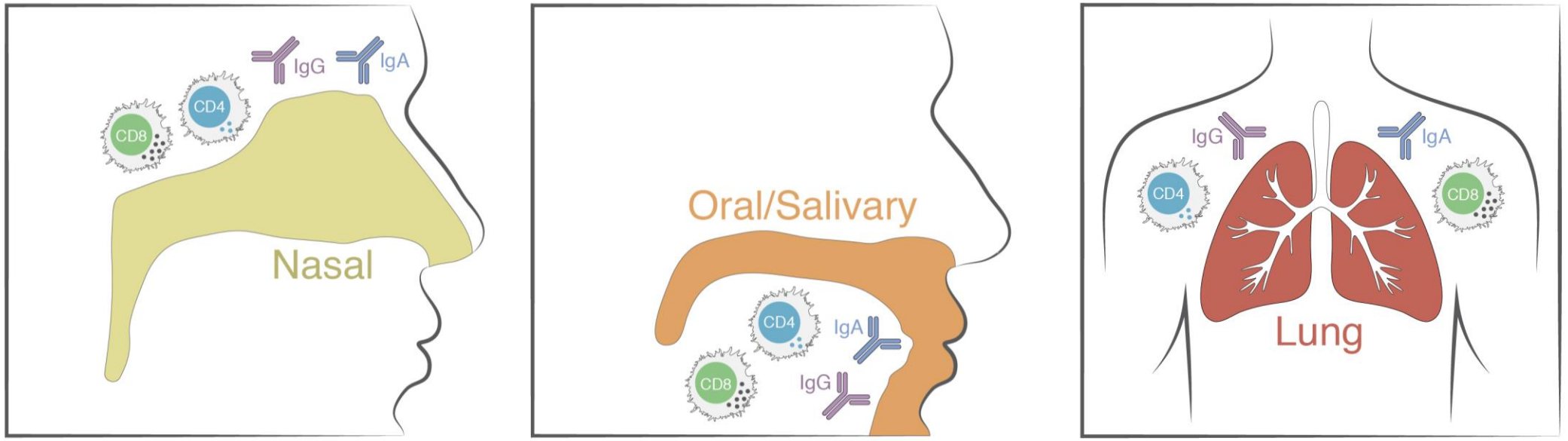
It is all a race

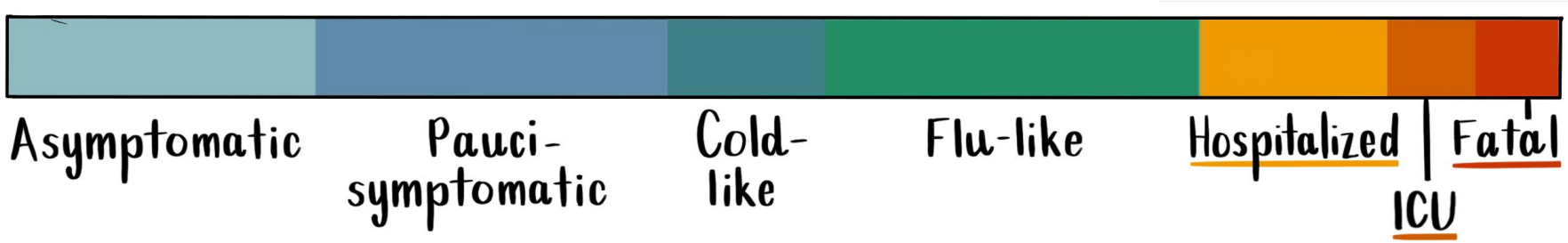
A race between the virus and your immune system.
Vaccines get rid of the race. You then have the headstart instead of the virus.

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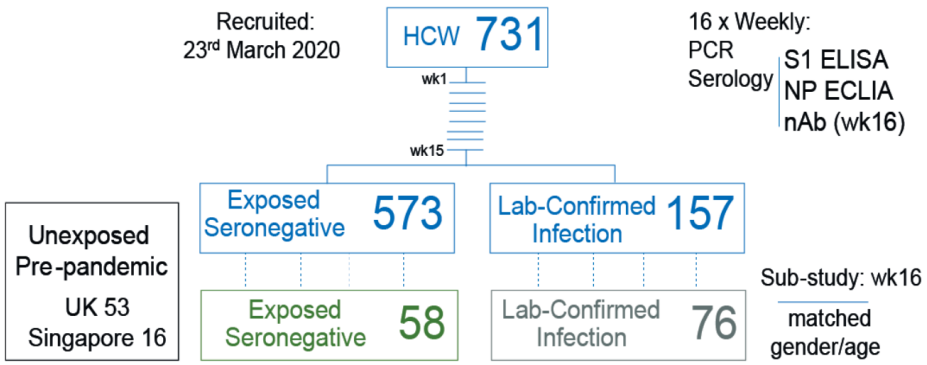


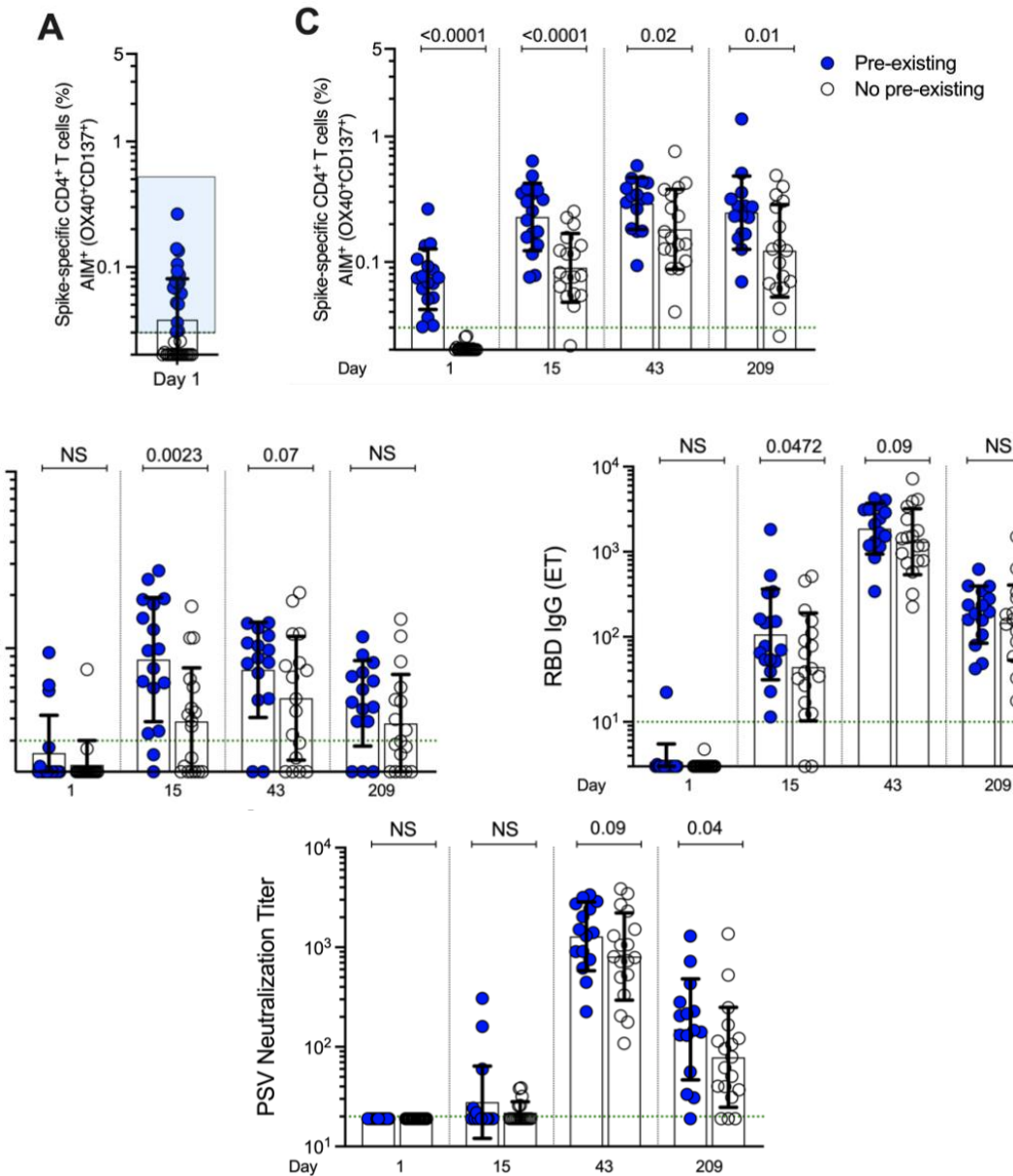
Sette and Crotty, Cell 2021

Evidence of T cell roles in prevention of symptomatic COVID-19

Three recent studies on pre-existing crossreactive memory T cells provide additional evidence of the value of T cell memory against COVID-19

- Weiskopf, Crotty, Sette and colleagues
- Thiel and colleagues
- Maini and colleagues





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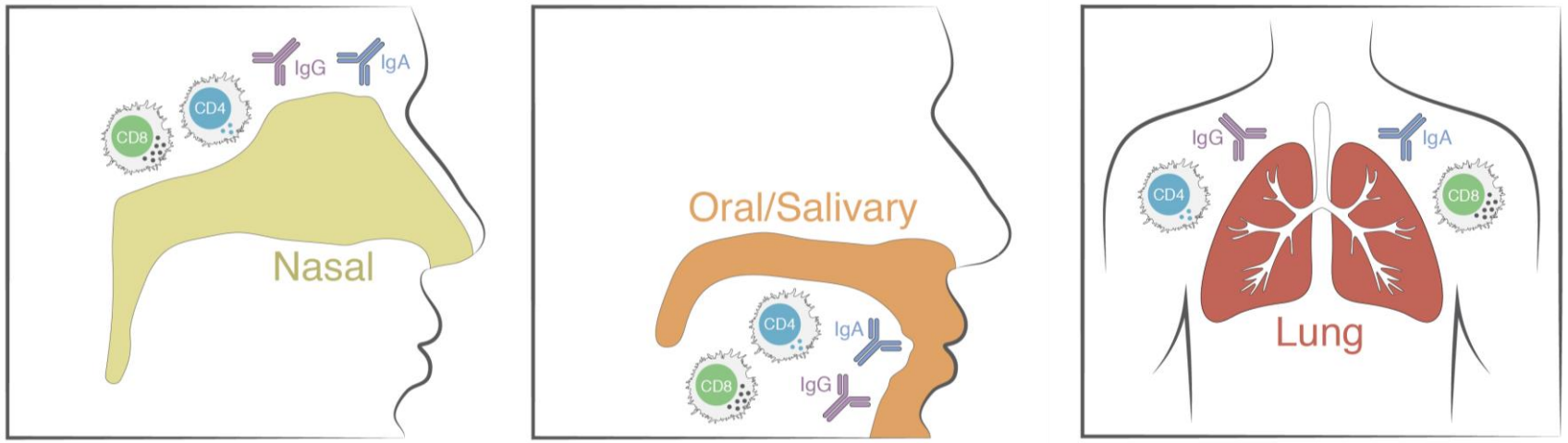
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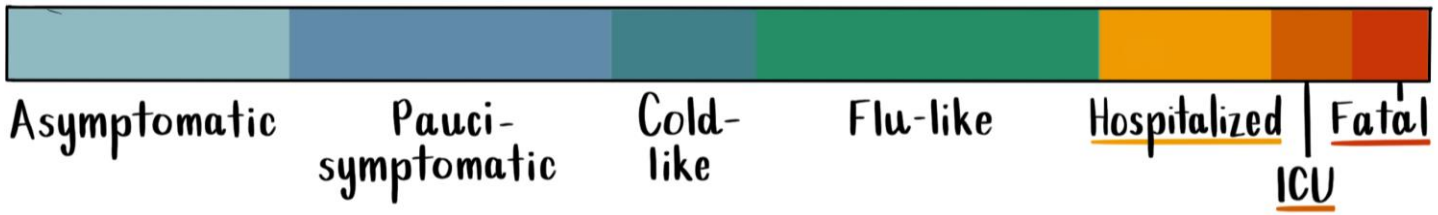
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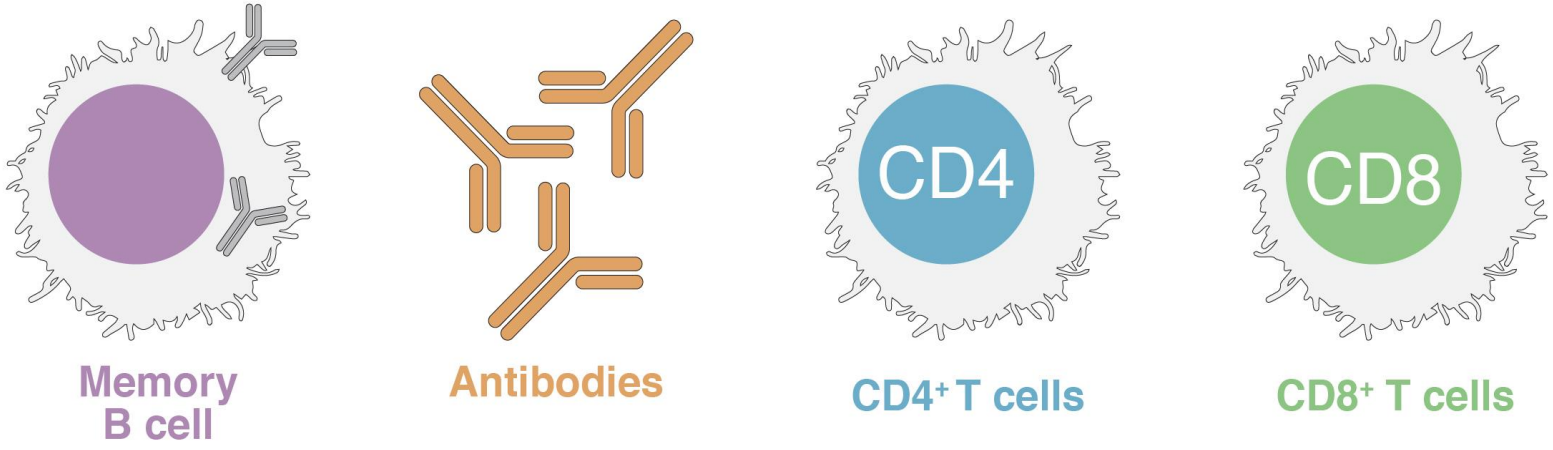
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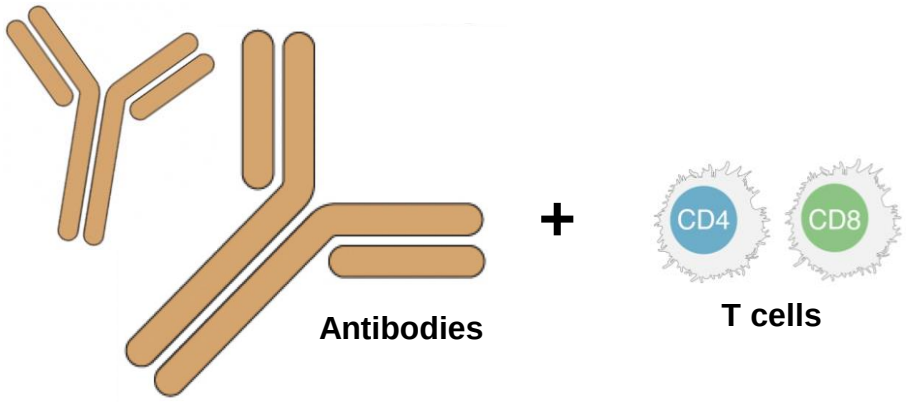
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Vaccine protection against SARS-CoV-2

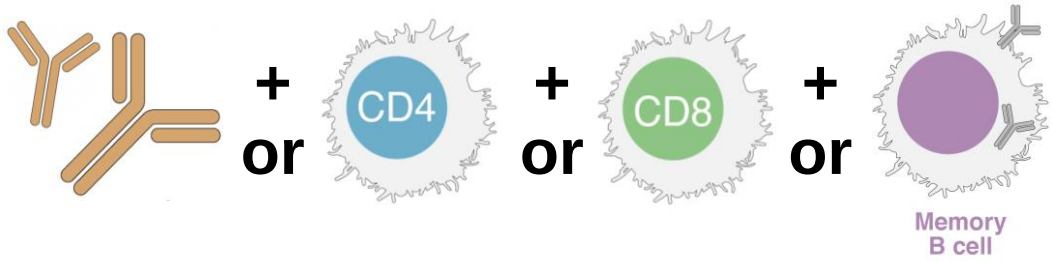
Protection against Detectable Infection



Major

Minor

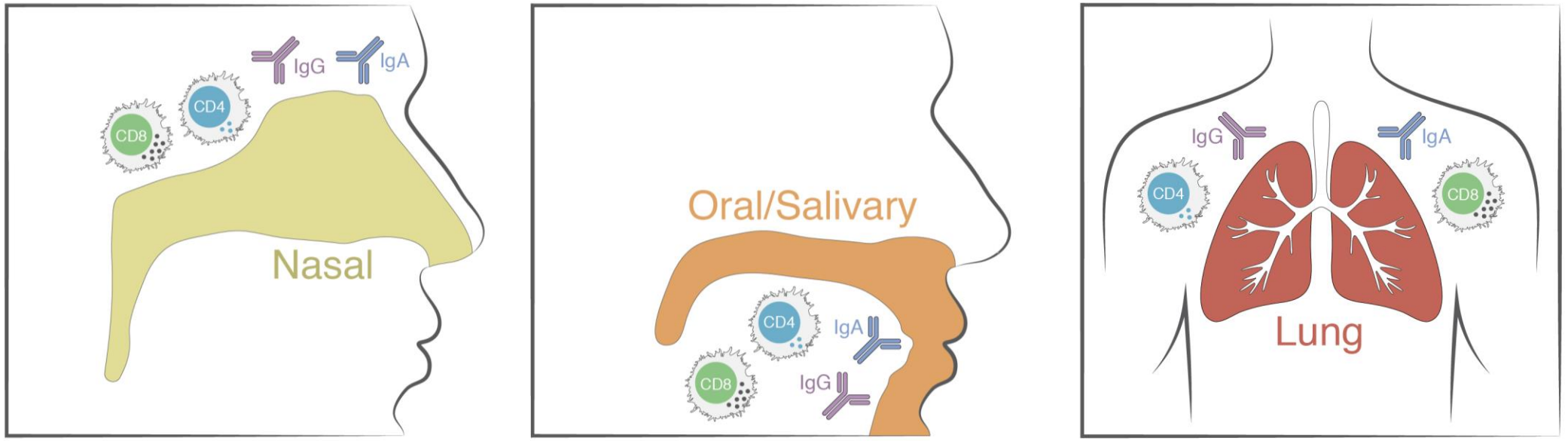
Protection against Hospitalizations & Deaths

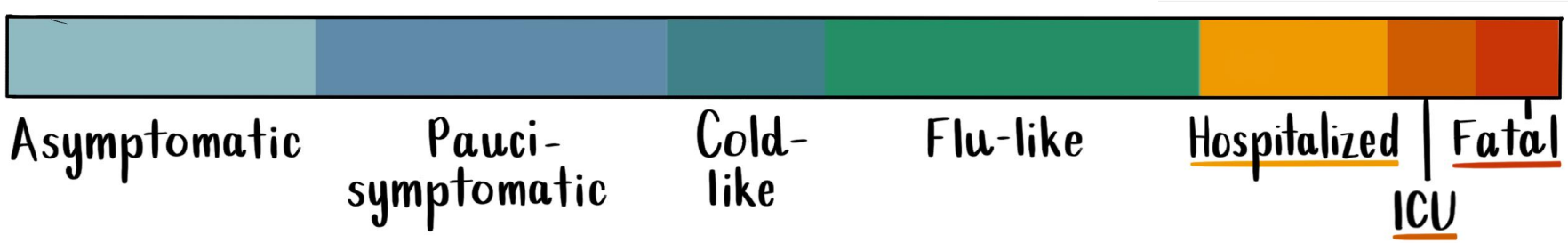


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Conditions where this may be important:

Natural immunity

- when antibody titers are low

Vaccine-generated immunity (currently used COVID vaccines)

- When antibody titers decline
- Immunocompromised or immunosuppressed individuals
- Different time windows post-vaccination
  - T cell and binding antibodies to RNA vaccines detected faster than neutralizing antibodies
  - Immune memory compartments can have substantially different kinetics
- neutralizing antibody escape variants (B.1.351 and J&J vaccine example?)

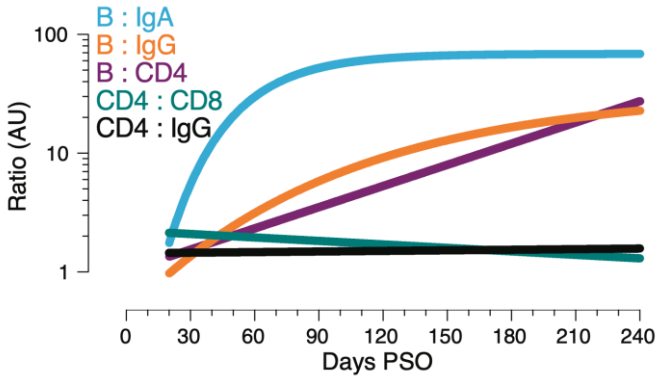
Novel vaccines with T cell dominant mechanisms of action

- T cell only vaccines or CD8 T cell dominant vaccines
- Mucosal vaccines that may have more complex mechanisms of action

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Dan et al. Science 2021

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T cell correlates of protection studies

- It is possible to do T cell correlates of protection studies in humans. This is a solved problem. The HIV Vaccine Trials Network (HVTN) has done this for over a decade.

- Even when T cells are mechanistically important for protection, evidence lags compared to antibodies because:
  - T cell studies are more resource intensive (~30 times)
  - T cell assays are more challenging to standardize across labs (live cells)
  - The simple passive transfer burden-of-proof available for antibodies is not available
  - Complexities of T cell contributions: CD4 T cells, CD8 T cells, subsets, functionalities, tissue location.

Q&A