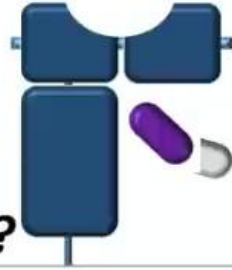


Why should current Covid-19 vaccines not be used for mass vaccination during a pandemic?



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Prophylactic vaccines are for use in...a conventional prophylactic setting, NOT in a pandemic setting

- Prophylactic vaccines should be administered before infectious exposure to:
 - ensure full-fledged protection
 - prevent exacerbation of disease (cfr. Ebola – ring vaccination)
 - *prevent immune escape* and hence, enhanced infectiousness or even, resistance to the vaccine
- Several cases of severe disease due to highly infectious variants have already occurred in young people
- Several cases of fully Covid-19 vaccinated people shedding highly infectious variants have already been reported (some of which have even developed mild symptoms)



Aren't these cases compelling enough to demonstrate how easily Covid-19 viruses can escape host immunity?

General Rule: Virus replication on background of suboptimal immune response enables immune escape of highly mutable viruses.



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Current Covid-19 vaccine technologies

- All of them are targeted at inducing specific Abs to S-protein (S1- RBD), so none of them prevents viral replication if Abs are too low in concentration or *affinity*
- ➔ They cannot control replication of more infectious CoV variants and may even drive immune escape (e.g., when fully vaccinated subjects are exposed to viral variants)
- Are they safe?
 - yes, at the level of the individual
 - absolutely not, for human populations exposed to Covid-19 pandemic
- Are they efficacious for protecting against disease?
 - yes, at the level of the individual
 - absolutely not, for human populations exposed to Covid-19 pandemic



Abs: Antibodies

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Gaps in our understanding of the natural course of viral pandemics

NACs*:

- Ag-nonspecific killing via natural Abs (NABs) and NK cells provide natural immunity

nonNACs**:

- Contract disease because of weak innate immunity
- Ag-specific killing (neutralization) via 'adaptive' Abs → protection
- Susceptible to disease when Ab titers wane



- Q: - Why does natural (i.e., w/o human intervention) viral pandemic comprise 3 waves?
- Why does 2nd wave typically hit younger people?
 - Why / how does the virus re-emerge to become seasonal?



Ag: Antigen; Abs: Antibodies

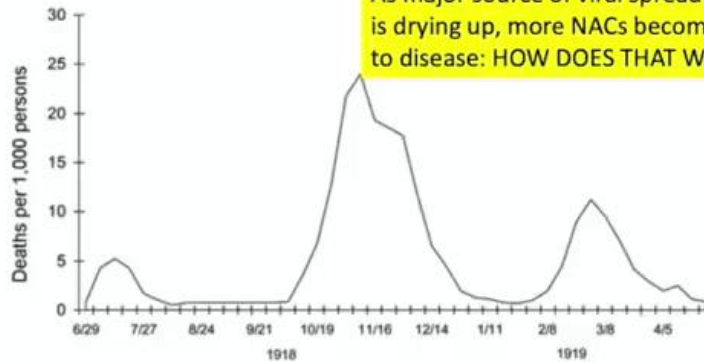
*NACs: Natural asymptomatic carriers ; refers to subjects who do not develop any clinical symptoms at all, or develop at most mild disease (involving upper respiratory airways only), after PRIMARY CoV infection

**nonNACs: Relates to subjects who develop severe Covid-19 symptoms after PRIMARY infection

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The current COVID-19 pandemic is often compared to the 1918 H1N1 influenza pandemic

For example, the 1889-92 influenza outbreak had three distinct waves, which differed in their virulence. The second wave was much more severe, particularly in younger adults.



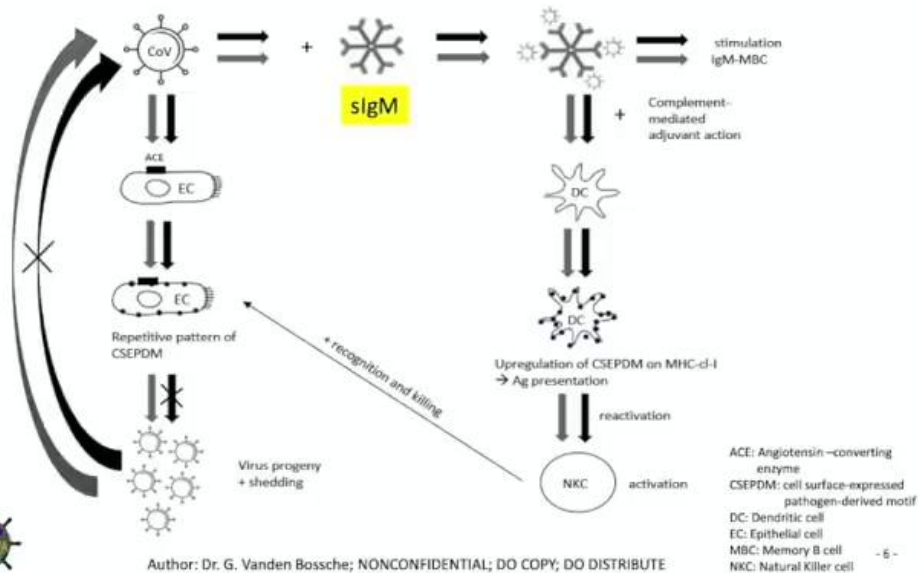
As major source of viral spread (nonNACs) is drying up, more NACs become susceptible to disease: HOW DOES THAT WORK?

Three waves of death: weekly combined influenza and pneumonia mortality, United Kingdom, 1918-1919. The waves were broadly the same globally during the pandemic. *Communicable Disease Control: 1918 Influenza: the Mother of All Pandemics. Strategic Infect Dis, 2016, 12(1):1-22, 12, 12, 12*

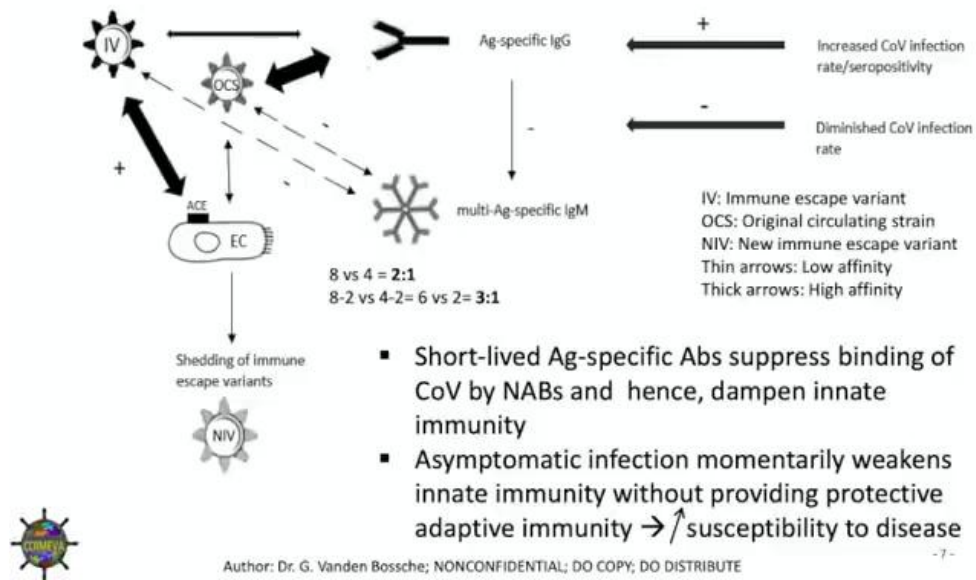
The current COVID-19 pandemic is often compared to the 1918 H1N1 influenza pandemic, which had three distinct waves over the course of a year. The proportion of influenza patients who were severely ill or died was much higher in the last two waves compared to the first.



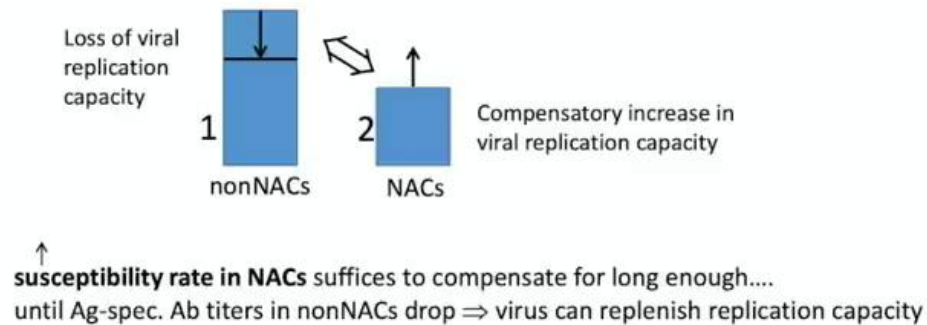
Abrogation of viral infection in NACs (after short-lived virus replication) is mediated by innate immunity



Abrogation of viral infection at an early stage of infection is the virus' secret weapon to ensure its own perpetuation

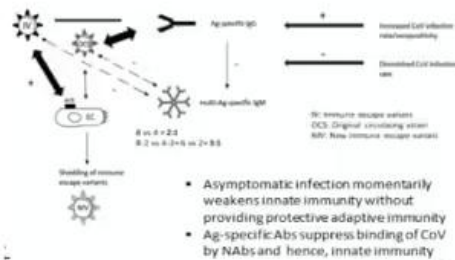


Increasing CoV infection rates promote enhancement of innate immune suppression in NACs (→ more susceptible to disease)



Containment measures and vaccination of NACs jeopardize capacity for viral replication

Abrogation of viral infection at an early stage of infection is the virus' secret weapon to ensure its own perpetuation



Abrogation of viral infection at an early stage of infection is the virus' secret weapon to ensure its own perpetuation **while leaving the door open for increasing its infectiousness when infection rates drop**

Since virus replication in NACs is under control of (innate) immune system, the virus can compensate for loss of replication/transmission capacity by enhancing infectiousness through selective immune escape

↑ viral infectiousness in NACs suffices to compensate for long enough... until Ag-spec. Ab titers in nonNACs drop

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But what if these Ab titers don't drop??

- Steady S-spec. Ab titers (VACCINATION!) in nonNACs will result in further increase in viral infectiousness in NACs... until 'return' on escape mutations in nonNACs becomes relatively more profitable for the virus



- RBD-specific escape mutations enable virus to rebuild sufficient capacity for viral replication in nonNACs. The resulting immune escape variants are now resistant to the vaccine.

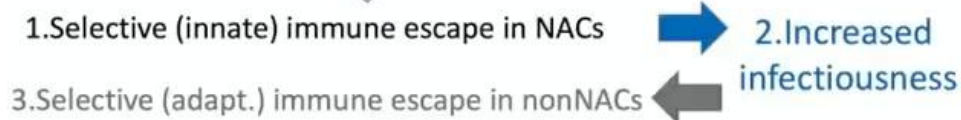


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Increasing infection/ seropositivity rates in NACs and nonNACs promote immune escape

- Enhanced infection rates lead to increased rates of transient seropositivity in NACs; seropositivity suppresses innate immunity **because Ag-specific Abs outcompete NABs for binding to CoV and prevent training of innate immune system**



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Strange observations during ongoing Covid-19 pandemic..

- Untypical course/ waves of pandemic
- Emergence of several much more infectious strains
- Viral shedding (of more infectious variants) in fully vaccinated subjects



Selective (S/ RBD) protein-directed) immune escape

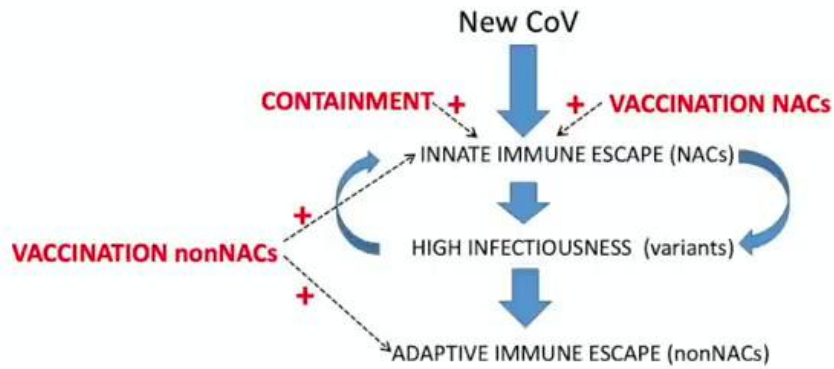


S: Spike protein
RBD: Receptor-binding domain

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Mass containment measures and mass vaccination in NACs accelerates INNATE immune escape whereas mass vaccination of nonNACs accelerates INNATE and ADAPTIVE immune escape



If needed, both NACs and nonNACs can serve as a potential source of immune escape upon human intervention in natural CoV pandemic

