Twitter Thread by Overshoot

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From "Distinct evolution of infection-enhancing and neutralizing epitopes in the spike protein of SARS-CoV-2 variants":

"Several pieces of evidence strongly argue in favor of an ADE issue for SARS-CoV-2."

https://t.co/GGDPNqTjzm

Abstract

Objectives. The efficiency of Covid-19 vaccination is determined by cellular and humoral immune responses, and for the latter, by the balance between neutralizing and infection-enhancing antibodies. Here we analyzed the evolution of neutralizing and facilitating epitopes in the spike protein among SARS-CoV-2 variants. **Methods.** Amino acid alignments were performed on 929,203 spike sequences over the 4 last months. Molecular modeling studies of the N-terminal domain (NTD) and rod-like regions of the spike protein were performed on a representative panel of SARS-CoV-2 variants that were structurally compared with the original Wuhan strain. **Results.** D614, which belongs to an antibody-dependent-enhancement (ADE) epitope common to SARS-CoV-1 and SARS-CoV-2, has rapidly mutated to D614G in the first months of 2020, explaining why ADE has not been detected following mass vaccination. We show that this epitope is conformationally linked to the main ADE epitope of the SARS-CoV-2 NTD which is highly conserved among most variants. In contrast, the neutralizing epitope of the NTD showed extensive variations in SARS-CoV-2 variants. **Conclusions.** This molecular epidemiology study coupled with structural analysis of the spike protein indicates that the balance between facilitating and neutralizing antibodies in vaccinated people is in favor of neutralization for the Wuhan strain, α and β variants, but not for γ, δ, λ and μ. The evolution of SARS-CoV-2 has dramatically affected the ADE/neutralization balance which is nowadays in favor of ADE. Future vaccines should consider these data to design new formulations adapted to SARS-CoV-2 variants and lacking ADE epitopes in the spike protein.

> "Neutralizing antibodies (Delta Variant) have a decreased affinity for the spike protein, whereas facilitating antibodies display a strikingly increased affinity. Thus, ADE may be a concern for people receiving vaccines based on the original Wuhan."https://t.co/yFIwImVbQY pic.twitter.com/psYfA2OfMA
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> — Overshoot (@Overshoooot) August 12, 2021

From "Anti-SARS-CoV-2 receptor-binding domain antibody evolution after mRNA vaccination":

"Antibodies selected over time by natural infection have greater potency and breadth than antibodies elicited by vaccination."

SARS-CoV-2-naive individuals. Between prime and boost, memory B cells produce antibodies that evolve increased neutralizing activity, but there is no further increase in potency or breadth thereafter. Instead, memory B cells that emerge five months after vaccination of naive individuals express antibodies that are similar to those that dominate the initial response. While individual memory antibodies selected over time by natural infection have greater potency and breadth than antibodies elicited by vaccination, the overall neutralizing potency of plasma is greater following vaccination. These results suggest that boosting vaccinated individuals with currently available mRNA vaccines will increase plasma neutralizing activity but may not produce antibodies with equivalent breadth to those obtained by vaccinating convalescent individuals.

From "The SARS-CoV-2 Delta variant is poised to acquire complete resistance to wild-type spike vaccines":

"Additional immunization of the spike protein derived from SARS-CoV-2 variants may boost enhancing antibodies more than the neutralizing antibodies."

Abstract:
mRNA-based vaccines provide effective protection against most common SARS-CoV-2 variants. However, identifying likely breakthrough variants is critical for future vaccine development. Here, we found that the Delta variant completely escaped from anti-N-terminal domain (NTD) neutralizing antibodies, while increasing responsiveness to anti-NTD infectivity-enhancing antibodies. Although Pfizer-BioNTech BNT162b2-immune sera neutralized the Delta variant, when four common mutations were introduced into the receptor binding domain (RBD) of the Delta variant (Delta 4+), some BNT162b2-immune sera lost neutralizing activity and enhanced the infectivity. Unique mutations in the Delta NTD were involved in the enhanced infectivity by the BNT162b2-immune sera. Sera of mice immunized by Delta spike, but not wild-type spike, consistently neutralized the Delta 4+ variant without enhancing infectivity. Given the fact that a Delta variant with three similar RBD mutations has already emerged according to the GISAID database, it is necessary to develop vaccines that protect against such complete breakthrough variants.

From "Increases in COVID■19 are unrelated to levels of vaccination across 68 countries and 2947 counties in the United States":

"There appears to be no discernable relationship between percentage of population fully vaccinated and new COVID-19 cases."

Findings

At the country-level, there appears to be no discernable relationship between percentage of population fully vaccinated and new COVID-19 cases in the last 7 days (Fig. 1). In fact, the trend line suggests a marginally positive association such that countries with higher percentage of population fully vaccinated have higher COVID-19 cases per 1 million people. Notably, Israel with over 60% of their population fully vaccinated had the highest COVID-19 cases per 1 million people in the last 7 days. The lack of a meaningful association between percentage population fully vaccinated and new COVID-19 cases is further exemplified, for instance, by comparison of Iceland and Portugal. Both countries have over 75% of their population fully vaccinated and have more COVID-19 cases per 1 million people than countries such as Vietnam and South Africa that have around 10% of their population fully vaccinated.

From "In vitro virucidal activity of povidone iodine gargle and mouthwash against SARS-CoV-2: implications for dental practice":

"PVP-I (1%) gargle and mouthwash showed 99.99% kill rate of SARS-CoV-2 in vitro within 15 seconds of contact in clean and dirty conditions."

Key points

Close contact and potential for aerosol generation increase risk of SARS-CoV-2 exposure during medical and dental procedures.	Pre-procedural mouth rinses are recommended as an additional measure to reduce cross-infection risk in dental settings.	PVP-I (1%) gargle and mouthwash showed 99.99% kill rate of SARS-CoV-2 *in vitro* within 15 seconds of contact in clean and dirty conditions.	The use of PVP-I-containing pre-procedural mouth rinse to reduce oral viral load could be recommended in addition to other protective measures.

Abstract

Introduction Virus particles in respiratory droplets and aerosols generated during medical/dental procedures are a potential source of SARS-CoV-2 cross infection. In the dental setting, oral decontamination could be an important adjunct to personal protective equipment and is recommended by a number of national COVID-19 guidance documents for dental settings.

Aim To assess the *in vitro* virucidal activity of an oral povidone iodine (PVP-I) product against SARS-CoV-2.

Material and methods BETADINE gargle and mouthwash (1% PVP-I) was tested against SARS-CoV-2 virus under both clean and dirty conditions using a suspension assay based on EN14476 methodology. Virucidal activity of the product, undiluted and at 1:2 dilution, was tested at contact times of 15, 30 and 60 seconds. Viral titres were calculated using the Spearman-Kärber method and reported as median tissue culture infectious dose ($TCID_{50}$/ml).

Results The undiluted product achieved >5 log10 reduction in viral titres compared to the control at 15, 30 and 60 seconds under both clean and dirty conditions. At a twofold dilution (0.5% PVP-I), the test product demonstrated >4 log10 kill at 15 seconds and >5 log10 kill at 30 and 60 seconds in both clean and dirty conditions.

Conclusion PVP-I gargle and mouthwash product, undiluted and at 1:2 dilution, demonstrated potent and rapid virucidal activity (≥4 log10 reduction of viral titre) in 15 seconds against SARS-CoV-2 *in vitro*. The PVP-I gargle and mouthwash product is widely available and could be readily integrated into infection control measures during dental treatment including pre-procedural oral decontamination.

From "Transmission potential of vaccinated and unvaccinated persons infected with the SARS-CoV-2 Delta variant in a federal prison":

A total of 978 specimens were provided by 95 participants, of whom 78 (82%) were fully vaccinated and 17 (18%) were not fully vaccinated. No significant differences were detected in duration of RT-PCR positivity among fully vaccinated participants (median: 13 days) versus those not fully vaccinated (median: 13 days; p=0.50), or in duration of culture positivity (medians: 5 days and 5 days; p=0.29). Among fully vaccinated participants, overall duration of culture positivity was shorter among Moderna vaccine recipients versus Pfizer (p=0.048) or Janssen (p=0.003) vaccine recipients.

Conclusions

As this field continues to develop, clinicians and public health practitioners should consider vaccinated persons who become infected with SARS-CoV-2 to be no less infectious than unvaccinated persons. These findings are critically important, especially in congregate settings where viral transmission can lead to large outbreaks.

From "Vaccinated and unvaccinated individuals have similar viral loads in communities with a high prevalence of the SARS-CoV-2 delta variant":

Abstract

SARS-CoV-2 variant B.1.617.2 (delta) is associated with higher viral loads [1] and increased transmissibility relative to other variants, as well as partial escape from polyclonal and monoclonal antibodies [2]. The emergence of the delta variant has been associated with increasing case counts and test-positivity rates, indicative of rapid community spread. Since early July 2021, SARS-CoV-2 cases in the United States have increased coincident with delta SARS-CoV-2 becoming the predominant lineage nationwide [3]. Understanding how and why the virus is spreading in settings where there is high vaccine coverage has important public health implications. It is particularly important to assess whether vaccinated individuals who become infected can transmit SARS-CoV-2 to others. In Wisconsin, a large local contract laboratory provides SARS-CoV-2 testing for multiple local health departments, providing a single standard source of data using the same assay to measure virus burdens in test-positive cases. This includes providing high-volume testing in Dane County, a county with extremely high vaccine coverage. These PCR-based tests provide semi-quantitative information about the viral load, or amount of SARS-CoV-2 RNA, in respiratory specimens. Here we use this viral load data to compare the amount of SARS-CoV-2 present in test-positive specimens from people who self-report their vaccine status and date of final immunization, during a period in which the delta variant became the predominant circulating variant in Wisconsin. We find no difference in viral loads when comparing unvaccinated individuals to those who have vaccine “breakthrough” infections. Furthermore, individuals with vaccine breakthrough infections frequently test positive with viral loads consistent with the ability to shed infectious viruses. Our results, while preliminary, suggest that if vaccinated

From "No Significant Difference in Viral Load Between Vaccinated and Unvaccinated, Asymptomatic and Symptomatic Groups Infected with SARS-CoV-2 Delta Variant":

"Over 20% of positive, vaccinated individuals had low Ct-values (<20), a third of which were asymptomatic when tested."

Abstract: We found no significant difference in cycle threshold values between vaccinated and unvaccinated, asymptomatic and symptomatic groups infected with SARS-CoV-2 Delta. Given the substantial proportion of asymptomatic vaccine breakthrough cases with high viral levels, interventions, including masking and testing, should be considered for all in settings with elevated COVID-19 transmission.

From: "Low neutralizing antibody titers against the Mu variant of SARS-CoV-2 in BNT162b2 vaccinated individuals."

"The Mu variant remarkably escapes from neutralizing antibodies elicited by the BNT162b2 vaccine"

Highlights

- Mu and Gamma variants represented 49% and 25% of cases in Colombia by August 2021.
- Increased proportion of SARS-COV-2 cases were mostly associated with Mu variant, despite being detected simultaneously with the VOC Gamma
- The Mu variant remarkably escapes from neutralizing antibodies elicited by the BNT162b2-vaccine
- Laboratory studies of neutralizing antibodies are useful to determine the efficacy of SARS-CoV-2 vaccines against VOC and VOI.

From "Ineffective neutralization of the SARS-CoV-2 Mu variant by convalescent and vaccine sera":

"We demonstrate that the Mu variant is highly resistant to sera from COVID-19 convalescents and BNT162b2 vaccinated individuals."

Abstract

On August 30, 2021, the WHO classified the SARS-CoV-2 Mu variant (B.1.621 lineage) as a new variant of interest. The WHO defines “comparative assessment of virus characteristics and public health risks” as primary action in response to the emergence of new SARS-CoV-2 variants. Here, we demonstrate that the Mu variant is highly resistant to sera from COVID-19 convalescents and BNT162b2-vaccinated individuals. Direct comparison of different SARS-CoV-2 spike proteins revealed that Mu spike is more resistant to serum-mediated neutralization than all other currently recognized variants of interest (VOI) and concern (VOC). This includes the Beta variant (B.1.351) that has been suggested to represent the most resistant variant to convalescent and vaccinated sera to date (e.g., Collier et al, Nature, 2021; Wang et al, Nature, 2021). Since breakthrough infection by newly emerging variants is a major concern during the current COVID-19 pandemic (Bergwerk et al., NEJM, 2021), we believe that our findings are of significant public health interest. Our results will help to better assess the risk posed by the Mu variant for vaccinated, previously infected and naïve populations.

From "Characterization of the immune resistance of SARS-CoV-2 Mu variant and the immunity induced by Mu infection.":

"Pronounced resistance of Mu variant against neutralizing antibodies is attributed to these two mutations (YY144-145TSN and E484K)."

Abstract

We have revealed that the SARS-CoV-2 Mu variant is highly resistant to COVID-19 convalescent sera and vaccine sera.[1] However, it remains unclear how the immune resistance of the Mu variant is determined. Also, although the Mu variant is highly resistant to the sera obtained from COVID-19 convalescent during early pandemic (i.e., infected with prototypic virus) and vaccinated individuals (i.e., immunized based on prototypic virus), it was unaddressed how the convalescent sera from Mu-infected individuals function. In this study, we revealed that the two mutations in the spike protein of Mu variant, YY144-145TSN and E484K, are responsible for the potent immune resistance of Mu variant. Additionally, we showed that the convalescent sera obtained from the Mu-infected individuals can be broadly antiviral against the Mu variant as well as other SARS-CoV-2 variants of concern/interest. Our findings suggest that developing novel vaccines based on the Mu variant can be more effective against a broad range of SARS-CoV-2 variants.

From "Infection-enhancing anti-SARS-CoV-2 antibodies recognize both the original Wuhan/D614G strain and Delta variants. A potential risk for mass vaccination?":

"ADE is a potential concern for vaccines. ADE of delta variants is a potential risk for current vaccines."

domain. As the NTD is also targeted by neutralizing antibodies, our data suggest that the balance between neutralizing and facilitating antibodies in vaccinated individuals is in favor of neutralization for the original Wuhan/D614G strain. However, in the case of the Delta variant, neutralizing antibodies have a decreased affinity for the spike protein, whereas facilitating antibodies display a strikingly increased affinity. Thus, ADE may be a concern for people receiving vaccines based on the original Wuhan strain spike sequence (either mRNA or viral vectors). Under these circumstances, second generation vaccines with spike protein formulations lacking structurally-conserved ADE-related epitopes should be considered.

From "COVID-19: Stigmatising the unvaccinated is not justified":

"There is increasing evidence that vaccinated individuals continue to have a relevant role in transmission. Ct values were similarly low between people who were fully vaccinated and people who were unvaccinated."

COVID-19: stigmatising the unvaccinated is not justified

In the USA and Germany, high-level officials have used the term pandemic of the unvaccinated, suggesting that people who have been vaccinated are not relevant in the epidemiology of COVID-19. Officials' use of this phrase might have encouraged one scientist to claim that "the unvaccinated threaten the vaccinated for COVID-19".[1] But this view is far too simple.

There is increasing evidence that vaccinated individuals continue to have a relevant role in transmission.

From "Risk of rapid evolutionary escape from biomedical interventions targeting SARS-CoV-2 spike protein":

"If new strains of SARS-CoV-2 are antigenically distinct, this may lead to risk of ADE as ADE involves antibodies that bind to the pathogen but fail to neutralize it."

Abstract

The spike protein receptor-binding domain (RBD) of SARS-CoV-2 is the molecular target for many vaccines and antibody-based prophylactics aimed at bringing COVID-19 under control. Such a narrow molecular focus raises the specter of viral immune evasion as a potential failure mode for these biomedical interventions. With the emergence of new strains of SARS-CoV-2 with altered transmissibility and immune evasion potential, a critical question is this: how easily can the virus escape neutralizing antibodies (nAbs) targeting the spike RBD? To answer this question, we combined an analysis of the RBD structure-function with an evolutionary modeling framework. Our structure-function analysis revealed that epitopes for RBD-targeting nAbs overlap one another substantially and can be evaded by escape mutants with ACE2 affinities comparable to the wild type, that are observed in sequence surveillance data and infect cells *in vitro*. This suggests that the fitness cost of nAb-evading mutations is low. We then used evolutionary modeling to predict the frequency of immune escape before and after the widespread presence of nAbs due to vaccines, passive immunization or natural immunity. Our modeling suggests that SARS-CoV-2 mutants with one or two mildly deleterious mutations are expected to exist in high numbers due to neutral genetic variation, and consequently resistance to vaccines or other prophylactics that rely on one or two antibodies for protection can develop quickly -and repeatedly- under positive selection. Predicted resistance timelines are comparable to those of the decay kinetics of nAbs raised against vaccinal or natural antigens, raising a second potential mechanism for loss of immunity in the population. Strategies for viral elimination should therefore be diversified across molecular targets and therapeutic modalities.

From "The epidemiological relevance of the COVID-19 vaccinated population is increasing":

"Decision makers assume that the vaccinated can be excluded as a source of transmission. It appears to be grossly negligent to ignore the vaccinated population
as a source of transmission."

The epidemiological relevance of the COVID-19-vaccinated population is increasing

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High COVID-19 vaccination rates were expected to reduce transmission of SARS-CoV-2 in populations by reducing the number of possible sources for transmission and thereby to reduce the burden of COVID-19 disease. Recent data, however, indicate that the epidemiological relevance of COVID-19 vaccinated individuals is increasing. In the UK it was described that secondary attack rates among household contacts exposed to fully vaccinated index cases was similar to household contacts exposed to unvaccinated index cases (25% for vaccinated vs 23% for unvaccinated). 12 of 31 infections in fully vaccinated household contacts (39%) arose from fully vaccinated epidemiologically linked index cases. Peak viral load did not differ by vaccination status or variant type [1]. In Germany, the rate of symptomatic COVID-19 cases among the fully vaccinated ("breakthrough infections") is reported weekly since 21. July 2021 and was 16.9% at that time among patients of 60 years and older [2]. This proportion is increasing week by week and was 58.9% on 27. October 2021 (Figure 1) providing clear evidence of the increasing relevance of the fully vaccinated as a possible source of transmission. A similar situation was described for the UK. Between week 39 and 42, a total of 100.160 COVID-19 cases were reported among citizens of 60 years or older. 89.821 occurred among the fully vaccinated (89.7%), 3.395 among the unvaccinated (3.4%) [3]. One week before, the COVID-19 case rate per 100.000 was higher among the subgroup of the vaccinated compared to the subgroup of the unvaccinated in all age