THE BEST OF THE WEEK (06 feb – 19 feb 2023)

Sacco C. et al.

Impatto della vaccinazione e della pregressa diagnosi sul rischio di infezione e di malattia severa associata a SARS-CoV-2: un'analisi dei casi diagnosticati nel mese di ottobre 2022

https://www.iss.it/-/impatto-della-vaccinazione-e-della-pregressa-diagnosi-sul-rischio-di-infezione-e-di-malattia-severa-associata-a-sars-cov-2-un-analisi-dei-casi-diagnosticati-nel-mese-di-ottobre-2022

Abstract

In Italia, l'epidemia di infezioni da SARS-CoV-2 nel corso del 2022 è stata influenzata dalla predominanza della variante Omicron, caratterizzata da alta trasmissibilità, e dalla progressiva eliminazione di quasi tutte le misure non farmacologiche di prevenzione. La combinazione di questi due elementi ha determinato una notevole circolazione virale di SARS-CoV-2 con oltre 24,5 milioni di casi da inizio epidemia. Dato l'alto numero di persone che ha superato almeno una infezione da SARS-CoV-2 e l'alta copertura vaccinale nella popolazione è necessario stimare il ruolo protettivo dell'immunità associata sia al vaccino che all'infezione pregressa nel prevenire l'infezione e la malattia severa da COVID-19. Il presente rapporto fornisce una stima del rischio di infezione e di malattia grave, per il mese di ottobre 2022, sulla base della vaccinazione e della precedente infezione. La massima protezione contro la diagnosi di infezione da SARS-CoV-2 e la malattia severa si realizza attraverso una immunità ibrida (l'effetto combinato della vaccinazione e della pregressa infezione) mentre livelli di rischio più alto si riscontrano sempre tra le persone non vaccinate e senza una precedente diagnosi di infezione. A parità di fascia di età e di pregressa infezione, si osserva una tendenza alla riduzione del rischio di malattia severa associata alla vaccinazione, in particolare se recente.

Bridget M. Kuehn.

US Life Expectancy in 2021 Lowest Since 1996

JAMA, January 2023; doi:10.1001/jama.2022.23562

Abstract

Life expectancy in the US decreased by about a half year between 2020 and 2021, from 77 years to 76.4 years, according to final 2021 mortality data from the National Center for Health Statistics. Life expectancy in 2021 was at its lowest level since 1996. The report attributed the drop mainly to increased deaths from COVID-19 and drug overdoses.

The 0.6-year drop between 2020 and 2021 followed a 1.8-year decrease in life expectancy between 2019 and 2020. The overall death rate from 2020 to 2021 in the US increased by 5.3%, from 835.4 to 879.7 deaths per 100 000 people. Life expectancy in the US decreased for every age group starting at age 1 year or older, but there was not a statistically significant change in infant mortality during this period.

The leading causes of death in 2021 were heart disease, cancer, and COVID-19. Deaths attributed to COVID-19 increased from 2020 to 2021 by 18.8%, from 350 831 to 416 893 deaths. Influenza and pneumonia dropped out of the top 10 causes of death in 2021, likely because of pandemic-related infection prevention precautions. Chronic liver disease moved up to the 9th leading cause of death. However, the other leading causes of death in the top 10, including unintentional injuries, stroke, chronic lower respiratory diseases, Alzheimer disease, and diabetes, remained the 4th to 8th leading causes of death, respectively, and kidney disease remained the 10th leading cause of death.
Some racial, ethnic, or other demographic groups were disproportionately affected by reductions in life expectancy. The gap in life expectancy between the sexes grew between 2020 and 2021. Males experienced a 0.7-year decrease in life expectancy, from 74.2 years to 73.5 years. Females, by contrast, saw a 0.6-year decrease, from 79.9 to 79.3 years. Death rates decreased for Black and Hispanic males by about 2% between 2020 and 2021 and stayed the same for Asian males and females. American Indian or Alaska Native males and females saw about a 6% to 7% increase in death rates, Black females saw a 1.3% increase, Hispanic females saw a 2.3% increase, and White males and females saw about a 7% increase in death rates.

Chaguza C et al.
Accelerated SARS-CoV-2 intrahost evolution leading to distinct genotypes during chronic infection
Cell, January 2023; doi.org/10.1016/j.xcrm.2023.100943
Abstract
The chronic infection hypothesis for novel SARS-CoV-2 variant emergence is increasingly gaining credence following the appearance of Omicron. Here we investigate intrahost evolution and genetic diversity of lineage B.1.517 during a SARS-CoV-2 chronic infection lasting for 471 days (and still ongoing) with consistently recovered infectious virus and high viral genome copies. During the infection, we find an accelerated virus evolutionary rate translating to 35 nucleotide substitutions per year, approximately two-fold higher than the global SARS-CoV-2 evolutionary rate. This intrahost evolution result in the emergence and persistence of at least three genetically distinct genotypes suggesting the establishment of spatially structured viral populations continually reseeding different genotypes into the nasopharynx. Finally, we track the temporal dynamics of genetic diversity to identify advantageous mutations and highlight hallmark changes for chronic infection. Our findings demonstrate that untreated chronic infections accelerate SARS-CoV-2 evolution, providing an opportunity for the emergence of genetically divergent variants.

El-Sadr W.M. et al.
Facing the New Covid-19 Reality
NEJM, february 2023; DOI: 10.1056/NEJMp2213920
We've come a long way. From the early, terrifying days of a rapidly spreading deadly infection to the current circumstances in which — despite a recent steep rise in transmission rates — Covid-19 has, for many people, become no more than an occasional inconvenience, involving a few days of symptoms and a short isolation period. It's clear that for many, if not most, people, SARS-CoV-2 infection no longer carries the same risks of

adverse outcomes as it did in the early months of the pandemic. These shifts have led to a widespread assumption, fueled by political and economic priorities, that the pandemic is behind us — that it's time to let go of caution and resume prepandemic life.

The reality, however, would starkly contradict such a belief. Covid-19 currently results in about 300 to 500 deaths per day in the United States — equivalent to an annual mortality burden higher than that associated with a bad influenza season. In addition, many people continue to face severe short- or long-term Covid-19 illness, including people who lack access to vaccines or treatment and those with underlying conditions that impair their immune response to vaccines or render them especially vulnerable to Covid-associated complications. The ever-looming threat of the evolution of a new variant, one that can evade our vaccines and antivirals, remains very real. These facts support the assumption that SARS-CoV-2 will continue to play a major role in our lives for the foreseeable future. This new reality compels us to navigate a more complex social, economic, political, and clinical terrain and to take to heart the lessons learned from the Covid-19 response thus far — both the successes and the missteps.

To date, monitoring of the effects of Covid-19 has rested on several epidemiologic and clinical measures, which have shaped the recommended or mandated protective actions. Most commonly, these measures have included estimated rates of Covid-19 cases, hospitalizations, and deaths; monitoring has also been conducted of circulating SARS-CoV-2 variants and their susceptibility to available vaccines and treatments.

Yet in the current situation, some of these traditional measures have limited value. For example, the availability of rapid antigen tests that can be conducted at home — the results of which often aren't captured by public health surveillance systems — challenges the validity of reported case numbers and transmission rates in some jurisdictions. There is therefore a need for unbiased monitoring of transmission and infection rates by means of regular testing of sentinel populations or randomly selected representative samples of the general population.1,2 Hospitalization and death rates are certainly more reliable measures than case rates, but these measures are limited by the fact that some hospitalized patients with SARS-CoV-2 infection have been admitted for other reasons and only incidentally tested positive. Furthermore, hospitalization and death are distal outcomes, so their rates have limited value for triggering early action to control the spread of infection and averting the consequences of a surge in cases. Other measures have gained prominence and now play a critical role in defining risk for infection or severe disease. Vaccine and booster coverage and availability and utilization of treatment for Covid-19 are critical variables that affect both the risk of severe illness or death from SARS-CoV-2 and health system capacity and access.

We have gained a deeper appreciation of the breadth of the pandemic's effects, beyond its obvious health effects. These effects have included loss of employment or housing, disruption of educational systems, and increased rates of food insecurity. Many of these negative social and economic effects were unintended results of mitigation measures, including stay-at-home orders, the shutting down of public venues, and transitions to remote learning. Although these measures were appropriate at the time, their effects weren't evenly distributed, with some communities facing disproportionate hardship, particularly historically marginalized racial and ethnic groups and communities with limited social and economic reserves. It is thus necessary to take into account the ways in which public health recommendations and policies may differentially affect various subgroups of the population. Government and nongovernmental entities need to create clear pathways for vulnerable populations to obtain access to the resources they need, including masks, vaccines, no-cost treatment, direct economic assistance, supplemental food, rent abatement, and Internet access to support virtual learning and remote access to health services.3 Such an approach requires that the federal government continue to invest in the Covid-19 response, since private-sector investment will be insufficient to meet all needs.4

One of the key challenges that the public health community faces as the pandemic evolves is the need to move away from universal recommendations, or population-wide prevention policy, toward a more differentiated or tailored approach — one that takes into account the characteristics of various communities and the pathogen. Relevant characteristics may include those that influence virus transmission or clinical outcomes, such as vaccine and booster coverage and risk factors for severe outcomes, including chronic medical conditions, racism and discrimination based on ethnicity, and lack of adequate health insurance. The implementation of tailored guidance for specific populations, however, is complicated by the legacy of glaring health disparities, the threat of stigmatization, and prevailing mistrust of authorities in some communities. Health-equity and antiracist principles and insights from the fields of health communication and behavioral science must therefore be taken into account from the start in the development and dissemination of recommendations and the implementation of programs and policies.3,5

There is much to lament in the politicization of the Covid-19 pandemic, the spread of disinformation and misinformation, the deep divisions within the U.S. population and, globally, in people's perceptions of the pandemic and willingness to trust guidance and embrace protective measures. These divisions should inspire a reexamination of the reasons that some public health recommendations fell flat, in addition to an acknowledgment that political expedience played a role in sowing mistrust. As the pandemic evolves, as the measures of its effects become more complex, and as guidance requires greater tailoring to specific populations, effective communication becomes even more important. Providing clear guidance, including explaining the rationale for various recommendations, acknowledging the social and economic trade-offs involved in complying with them, and offering people the resources they will need to effectively manage these trade-offs, would go a long way toward enabling the adoption of those recommendations.

Most important, attention to the engagement of trusted community leaders and spokespeople is required, as is listening authentically to communities from the start. Rather than focusing solely on what is being recommended, it's equally important for public health leaders to focus on how recommendations are communicated and disseminated. Early engagement of community representatives is critical so that various aspects of anticipated guidance can be discussed in detail, including rationales, trade-offs, and the most appropriate communication channels and formats. Engagement must not only come in the form of an emergency response, but must involve a consistent presence, which can then be leveraged and activated further during times of urgent need.

The current moment in the Covid-19 pandemic is a pivotal one. There is an urgent need to confront a future in which SARS-CoV-2 will remain with us, threatening the health and well-being of millions of people throughout the world. At the same time, it's important to acknowledge that objectively we are in a better place with regard to the virus than we've ever been and that in fact many people believe the pandemic is behind us. This reality compels us to avoid using alarmist language and to offer valid and feasible solutions to bring people along to a new, nonemergency phase of the pandemic. How we craft our policies, programs, and associated messaging in this context and who delivers the messages is as important as ever.

Bobrovitz N et al.

Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression

The Lancet, January 2023; doi.org/10.1016/S1473-3099(22)00801-5

Abstract

Background

The global surge in the omicron (B.1.1.529) variant has resulted in many individuals with hybrid immunity (immunity developed through a combination of SARS-CoV-2 infection and vaccination). We aimed to systematically review the magnitude and duration of the protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against infection and severe disease caused by the omicron variant.

Methods

For this systematic review and meta-regression, we searched for cohort, cross-sectional, and case–control studies in MEDLINE, Embase, Web of Science, ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials, the WHO COVID-19 database, and Europe PubMed Central from Jan 1, 2020, to June 1, 2022, using keywords related to SARS-CoV-2, reinfection, protective effectiveness, previous infection, presence of antibodies, and hybrid immunity. The main outcomes were the protective effectiveness against reinfection and against hospital admission or severe disease of hybrid immunity, hybrid immunity relative to previous infection alone, hybrid immunity relative to previous vaccination alone, and hybrid immunity relative to hybrid immunity with fewer vaccine doses. Risk of bias was assessed with the Risk of Bias In Non-Randomized Studies of Interventions Tool. We used log-odds random-effects meta-regression to estimate the magnitude of protection at 1-month intervals. This study was registered with PROSPERO (CRD42022318605).

Findings

11 studies reporting the protective effectiveness of previous SARS-CoV-2 infection and 15 studies reporting the protective effectiveness of hybrid immunity were included. For previous infection, there were 97 estimates (27 with a moderate risk of bias and 70 with a serious risk of bias). The effectiveness of previous infection against hospital admission or severe disease was 74·6% (95% CI 63·1–83·5) at 12 months. The effectiveness of previous infection against reinfection waned to 24·7% (95% CI 16·4–35·5) at 12 months. For hybrid immunity, there were 153 estimates (78 with a moderate risk of bias and 75 with a serious risk of bias). The effectiveness of hybrid immunity against hospital admission or severe disease was 97·4% (95% CI 91·4–99·2) at 12 months with primary series vaccination and 95·3% (81·9–98·9) at 6 months with the first booster vaccination after the most recent infection or vaccination. Against reinfection, the effectiveness of hybrid immunity following primary series vaccination waned to 41·8% (95% CI 31·5–52·8) at 12 months, while the effectiveness of hybrid immunity following first booster vaccination waned to 46·5% (36·0–57·3) at 6 months.

Interpretation

All estimates of protection waned within months against reinfection but remained high and sustained for hospital admission or severe disease. Individuals with hybrid immunity had the highest magnitude and durability of protection, and as a result might be able to extend the period before booster vaccinations are needed compared to individuals who have never been infected.

Cassandra Willyard

How quickly does COVID immunity fade? What scientists know Vaccination, infection with SARS-CoV-2 and a combination of both provide varying degrees of protection

Nature, February 2023; doi.org/10.1038/d41586-023-00124-y

Abstract

Three years into the pandemic, the immune systems of the vast majority of humans have learnt to recognize SARS-CoV-2 through vaccination, infection or, in many cases, both. But just how quickly do these types of immunity fade?

New evidence suggests that 'hybrid' immunity, the result of both vaccination and a bout of COVID-19, can provide partial protection against reinfection for at least eight months1. It also offers greater than 95% protection against severe disease or hospitalization for between six months and a year after an infection or vaccination, according to estimates from a meta-analysis2. Immunity acquired by booster vaccination alone seems to fade somewhat faster.

But the durability of immunity is much more complex than the numbers suggest. How long the immune system can fend off SARS-CoV-2 infection depends not only on how much immunity wanes over time but also on how well immune cells recognize their target. "And that has more to do with the virus and how much it mutates," says Deepta Bhattacharya, an immunologist at the University of Arizona College of Medicine in Tucson. If a new variant finds ways to escape the existing immune response, then even a recent infection might not guarantee protection.

Omicron era

Omicron has presented just such a scenario. In late 2021 and early 2022, the main Omicron subvariants that were causing infections were BA.1 and BA.2. By mid-2022, the BA.5 wave was gathering strength in some countries, raising the prospect that those who'd already had one round of Omicron could soon be exposed to another. Data are now providing a sense of the risk of reinfection over time.

In one study, researchers looking at Portugal's national database of infections studied vaccinated people who became infected during the BA.1/BA.2 wave. Analysis showed that 90 days after an infection, this population had high immune protection — their risk of becoming infected with BA.5 was just one-sixteenth that of people who had been vaccinated but never infected. After that, hybrid immunity against infection declined steeply for a few months and then stabilized, ultimately providing protection for eight months after infection, the duration of the study.

What the Omicron wave is revealing about human immunity

Another study looked at 338 vaccinated health-care workers in Sweden, some of whom had had a previous SARS-CoV-2 infection. The authors found that workers with hybrid immunity had some level of protection against infection with BA.1, BA.2 and BA.5 for at least eight months. Swabbing of these workers' noses revealed high levels of 'mucosal' antibodies, which are thought to be a better shield against infection than antibodies that circulate in the blood.

A study in Qatar compared the infection risks of people who had never caught SARS-CoV-2 with those of people who'd had a previous infection with Omicron or an earlier variant. Both groups included vaccinated and unvaccinated individuals. The results show that more recent infections provide greater protection than older ones in all cases. But because the virus kept evolving, the authors couldn't untangle whether those

differences were because of waning immunity, the virus's growing ability to evade the immune response or, more likely, a combination of the two.

Infection reprieve

Taken together, the studies suggest that hybrid immunity provides some protection against infection for at least seven or eight months, and probably longer. "That's pretty good," says Charlotte Thålin, an immunologist at the Karolinska Institute in Stockholm and an author of the Swedish study.

Other data suggest that in people whose immunity arises only from vaccination, a booster dose provides relatively short-lived protection against infection. Researchers in Israel studied more than 10,000 health-care workers who had not previously been infected; all received either three or four doses of the vaccine made by Pfizer and BioNTech5. The authors found that the fourth dose's efficacy against infection fell rapidly. In fact, after four months, the fourth dose was no better than three doses at preventing infection.

Immunity against Omicron from breakthrough infection could be a matter of timing

However, "we are talking just about what we call relatively mild disease", says study co-author GiliRegev-Yochay, an epidemiologist at Sheba Medical Center Tel Hashomer in Ramat Gan, Israel. None of the people in the study developed severe COVID-19.

What about those who haven't been vaccinated? Another study6 in Qatar suggests that if the virus doesn't change, infection-based immunity against reinfection can last up to three years. But that immunity can fade faster if the virus mutates. The authors studied data from unvaccinated people who were infected with a pre-Omicron variant. Fifteen months later, those infections were less than 10% effective at protecting against Omicron infection. And it is much riskier to rely on immunity from infection than to get immunized.

But it's nearly impossible to apply the study results to predict an individual's risk of becoming infected in future. Immunity depends on a variety of factors, including genetics, age and sex. And past risk of infection isn't necessarily a good predictor of the risk of future infection, because new variants are continually arising.

Booster break

How growing global hybrid immunity will affect the timing and frequency of infection surges isn't yet clear. Neither is it clear how this will influence health officials' decisions about when to offer future booster doses.

For people who are at high risk of developing severe COVID-19, it might make sense to get boosters frequently. Younger individuals without any risk factors who live in regions where the virus has been circulating freely "may already have very significant protection that may not require as frequent boosters", says LuísGraça, an immunologist in the Faculty of Medicine at the University of Lisbon and a co-author of the Portuguese study. Another option might be to give a booster when antibody levels fall below a certain threshold, says Regev-Yochay.

Thålin understands how frustrating the caveats and uncertainty can be, but says that researchers aren't likely to pin down an answer anytime soon. "The virus is evolving so fast," she says. "What's true today might not be true tomorrow?".

Pan Y. et al.

Characterisation of SARS-CoV-2 variants in Beijing during 2022: an epidemiological and phylogenetic analysis

The Lancet, February 2023; doi.org/10.1016/S0140-6736(23)00129-0

Abstract

Background

Due to the national dynamic zero-COVID strategy in China, there were no persistent local transmissions of SARS-CoV-2 in Beijing before December, 2022. However, imported cases have been frequently detected over the past 3 years. With soaring growth in the number of COVID-19 cases in China recently, there are concerns that there might be an emergence of novel SARS-CoV-2 variants. Routine surveillance of viral genomes has been carried out in Beijing over the last 3 years. Spatiotemporal analyses of recent viral genome sequences compared with that of global pooled and local data are crucial for the global response to the ongoing COVID-19 pandemic.

Methods

We routinely collected respiratory samples covering both imported and local cases in Beijing for the last 3 years (of which the present study pertains to samples collected between January and December, 2022), and then randomly selected samples for analysis. Next-generation sequencing was used to generate the SARS-CoV-2 genomes. Phylogenetic and population dynamic analyses were performed using high-quality complete sequences in this study.

Findings

We obtained a total of 2994 complete SARS-CoV-2 genome sequences in this study, among which 2881 were high quality and were used for further analysis. From Nov 14 to Dec 20, we sequenced 413 new samples, including 350 local cases and 63 imported cases. All of these genomes belong to the existing 123 Pango lineages, showing there are no persistently dominant variants or novel lineages. Nevertheless, BA.5.2 and BF.7 are currently dominant in Beijing, accounting for 90% of local cases since Nov 14 (315 of 350 local cases sequenced in this study). The effective population size for both BA.5.2 and BF.7 in Beijing increased after Nov 14, 2022.

Interpretation

The co-circulation of BF.7 and BA.5.2 has been present in the current outbreak since Nov 14, 2022 in Beijing, and there is no evidence that novel variants emerged. Although our data were only from Beijing, the results could be considered a snapshot of China, due to the frequent population exchange and the presence of circulating strains with high transmissibility.