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RESEARCH ARTICLE

What We Know about HV.1 (EG.5.1.6.1) SARS-CoV-2 Variant.

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ABSTRACT

Background: HV.1 (EG.5.1.6.1) was the dominant strain in the U.S. as of the end of second week of December 2023, according to the U.S. Centers for Disease Control and Prevention (CDC). The strain is a descendant of EG.5 family that was identified in China in February 2023 and was first detected in the United States in April 2023. 44 mutations in S-protein, 2 in Membrane and Envelope viral structures, 5 mutations in the Nucleocapsid, 21 mutations in Orf1a, 1 mutation in Orf3a, Orf6, Orf10, and 2 mutations in Orf8 virus genome open reading frames are reported. The symptoms of HV.1 are similar that of other Omicron variants, these include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea, but congestion, sore throat and dry cough seem to be the three most prominent symptoms right now. Since HV.1 belongs to the same family as XBB, health experts assumethat updated vaccines are expected to be effective against this new dominant subvariant.The only way to distinguish (COVID-19) from RSV and flu, both of which are now gaining steam, is by testing.

Aim: The purpose of the manuscript is to present a systematic review on the prevalence, structural, genomic, and pathogenic characteristics of HV.1 from October 1, 2023, as of December 31, 2023, emphasizing on the variant genetic characteristics, contagiousness, and potential pathogenicity.

Material and Methods: Original scientific articles published in Medline, Pubmed, Science Direct, Web of Science, Scopus, EBSCO and BioMed Central databases, official health organizations electronic publications, and specialized media in the subject, were electronically searched to accomplish the aim of the study. Articles published in any language were included from October 2023 to present using a variety of keywords in combination. The studies relevant to our review were analysed and compared.

Results and Discussion: HV.1 showed significantly lower plasma neutralisation titers compared with their parental strains after acquiring L452R and A475V mutations, explaining their growth advantages. A475V mutation also resulted in decreased binding affinity, enhancing immune evasion compared to HK.3 (XBB.1.5+FLip). However, the L452R mutation of HV.1 did not affect binding affinity. 44 mutations in S-protein, 2 in Membrane and Envelope viral structures, 5 in the Nucleocapsid, 21 in Orf1a, 1 mutation in Orf3a, Orf6, Orf10, and 2 in Orf8 virus genome open reading frames mutations are reported. These mutations give to HV.1 improved ability to enter the human cell, although no greater pathogenicity or severity of the symptoms.

Conclusions: The latest data from US-CDC in 2023, shows HV.1 as the second prevalent SARS-CoV-2 variant in the United States. HV.1 (XBB.1.9.2.5.1.6.1 or EG.5.1.6.1) in October 2023, quickly increase its prevalence and surpassed other variants, includingEG.5 (Eris) to become the most prevalent strain in USA until week ending on December 9, 2023. HV.1 has a similar transmission rate, exhibits a greater evasive capacity of immune-generated antibodies than EG.5.1* family of SARS-CoV-2, produce similar symptoms that of other Omicron variants, are expected not to produce an increase in hospitalizations and mortality rate and the SARS-CoV-2 vaccines recently developed by Pfizer and Moderna, must be effective against this Omicron subvariant.For now HV.1 does not seem harmful in terms of creating a deadly disease but is still contagious enough to not be ignored.
Keywords: HV.1, S-protein mutations, Orf mutations, Pathogenic Properties.

Introduction

HV.1 emerged in the United States at the end of September 2023 and has progressively made up a larger proportion of the circulating virus.

According to the Centers for Disease Control and Prevention, it overtook a related variant, EG.5, in late October 2023.

HV.1 (XBB.1.9.2.5.1.6.1 or EG.5.1.6.1) in October 2023, quickly increase its prevalence and surpassed other variants, includingEG.5 (Eris) to become the most prevalent strain in USA until week ending on December 9, 2023.

The US-CDC Nowcast Estimates in the United States for 12/10/2023-12/23/2023, shows HV.1 (22.1%) as the second prevalent SARS-CoV-2 variant in the United States, behind JN.1 (44.2%).

EG.5. was the dominant variant in the United States for much of the late summer, on October 7 and early fall.

As of December 30, 2023, accounts for just under five percent of cases.

Discussion

On October 7, 2023, Pledge Times, Health publishes the article[1] "COVID, HV.1 new variant: what we know, latest news", describing HV.1 is a new variant of COVID-19, to be precise "one of the subvariants of EG.5".

Massimo Ciccozzi, head of the Medical Statistics and Epidemiology Unit of the Faculty of Medicine and Surgery of the Bio-Medico Campus of Rome, commenting:

"In short, it doesn't mean that for this reason we are going backwards and that the virus, instead of attacking the upper airways, descends into the lungs again like at the beginning.

I don't believe it, because evolution always takes steps forward and never backwards", adds the expert.

"It could happen that the original EG5 variant stabilizes, as happened with Omicron, and creates a series of subvariants, like this one.

One thing is certain, however in terms of evasion of the immune system, Ciccozzi behaves like the entire family Omicron.

The only one that stands out a bit immunogenetically from all the others is BA.2.86, but HV.1 is a subvariant of EG5, so I wouldn't worry too much", he comments.

In the tracking of variants carried out by the Centers for Disease Control (CDC) at the end of September 2023, HV.1 went from 7-8% to 12.9% in the United States in two weeks, and it continues to grow.

On October 7, in the Breaking latest News[2] the HealthEditorial Staff published that the "strongly growing subvariant HV.1 is reminiscent of Delta and is spreading in theUnited Stateswhere, according to experts from the University of Arkansas, it could soon become dominant, overtaking Eris (EG.5) and Fornax (FL.1.5.1)".

HV.1 has been isolated particularly in New York and shows a slight advantage in terms of growth compared to the lineages circulating in New York.

At the moment it is still an acronym under observation in theUnited States, but if it continues to grow and attracts international attention.

HV.1 will also soon be renamed, like Triton, Cerberus, Kraken, Acturus, Eris, the latest arrival Pirola and the lesser known Fornax.

On October 14, Virginia Department of Health published "COVID-19 Variants, Subvariants, Drug Activity, and Information", updated October 13, 2023.

About HV.1 informs that according to CDC data as of October 14, 2023, the weighed estimate variant proportion in U.S. was 19.5%, only below EG.5 (23.6%).

As of 10/13/2023, major Omicron variants/subvariants in HHS Region 3 (includes VA, DE, Wash D.C., MD, PA, WV) include:

- EG.5 estimated prevalence 22.9%.
- HV.1 estimated prevalence 25.7%.
- FL.1.5.1 estimated prevalence 13.7%.
- XBB.1.16.6 est. prevalence 9.1%.
- HK.3 estimated prevalence 3.5%.
- XBB.2.3 estimated prevalence 3.6%.
- XBB.1.16.11 est. prevalence 2.4%.
- XBB.1.16 estimated prevalence 2.6%.

About the COVID-19 treatments:

- The three current antiviral drugs (Nirmatrelvir with Ritonavir [Paxlovid], Remdesivir [Veklury], and Molnupiravir [Lagevrio]) are expected to have activity against all current circulating variants.
- Oral Paxlovid continues to be NIH's first-choice drug and IV remdesivir the next preferred option for treatment of mild to moderate COVID-19 in high-risk outpatients. See the NIH Treatment Panel's section on Antiviral Agents, including Antibody Products.
- According to its EUA, Molnupiravir is a treatment option only if Paxlovid or Remdesivir are not appropriate medications for a patient, or they are not available.
- "Legacy" monoclonal antibodies (Bamlanivimab/Etesevimab ["Bam/Ete"], REGEN-COV [Casirivimab plus Imdevimab], Sotrovimab, Bebtelovimab), do NOT have an EUA for any current use including treatment of COVID-19 or postexposure prophylaxis. These drugs are not active against newer Omicron variants.

On October 18, Kristina Fiore, Director of Enterprise & Investigative Reporting, MedPage Today,published[3] "What to Know About the HV.1 Variant".

She note that for the 2-week period ending October 14, the CDC projects that theHV.1 variant opens in a new tab or windowwill account for nearly 20% of cases.

Only the EG.5 variant makes up a larger proportion of cases, estimated at 24%.

HV.1 jumped from an estimated prevalence of about 13% for the 2-week period ending September 30, according toCDC's variant proportions trackeropens in a new tab or window.

For the finalized reporting period just prior to that, HV.1 accounted for about 8% of cases.

Shishi Luo, Head of Infectious Diseases of Helix Company, which sequences SARS-CoV-2 in samples from both outpatients and hospitalized patients, said HV.1 hasn't raised any red flags yet.

The prevalence of HV.1 "in hospitalized patients is similar to the prevalence in non-hospitalized patients".

Luo toldMedPage Today, noting that the same is true for EG.5 and FL.1.5.1, estimated to be the third-most prevalent variant at this time.

"We're treating it as any other new variant, monitoring it and looking for signs that it will lead to more severe disease, or if it's more transmissible, so that healthcare workers can be prepared", Luo said.

Luo noted that HV.1 is a sublineage of XBB.1.9.2, so it is still within the Omicron family.

It's actually a direct descendant of EG.5, according to CDC's lineage tree.

Luo reiterated the importance of continued surveillance for new COVID variants, as well as for other respiratory pathogens including influenza and respiratory syncytial virus (RSV).

"We should monitor all of the respiratory viruses in the same way we currently monitor COVID, and that should help with hospital preparedness and resourcing".

On October 31st, The India Times staff published[4] "Coronavirus: New dominant COVID HV.1 variant is here; all you need to know about it".

The article emphasizes the new COVID-19 variant, HV.1, is becoming the dominating strain in circulation in the United States.

It made up just 0.5% of cases in late July and has now nearly overtaken EG.5, the dominant subvariant in the US since mid-August.

HV.1 is a mutation of EG.5, which was derived from the original XBB strain.

According to health experts, HV.1 is fairly similar to the other Omicron strains, despite having mutations that make it different from other sub variants.

As per reports, the severity of the HV.1 variant is expected to be the same as the other XBB-related sub variants.

Even though the rate of transmission of the HV.1 variant is high, it also doesn't seem to be causing more serious disease than other variants circulating, says William Schaffner, an infectious disease specialist and professor at the Vanderbilt University School of Medicine, quoted Prevention.

"I don't think people should be very concerned about this", he says.

The symptoms of the HV.1 variant are consistent with other COVID-19 symptoms so far.

According to CDC, these include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea.

Most of the common symptoms are similar to that of cold.

However, the severity of the symptoms, despite being similar to common cold, can vary from person to person.

The infection could be dangerous for someone who is immunocompromised.

The new COVID boosters from Pfizer and Moderna were updated to target XBB variants of the virus.

Experts believe these are likely to offer some form of added protection against HV.1, as the latest variant appears to be similar to those XBB variants targeted by the boosters.

Services, flagged a new mutation of COVID-19's omicron variant BA.2.86, called JN.1, in a report last week.

With limited information, they said they cannot comment on whether it will spread more widely as they are still determining its characteristics.

The varianthas been in circulation in 11 countries, namely the United Kingdom, Iceland, Portugal, Spain, among others.

On November 9, Cecelia Smith-Schoenwalder from U.S. News & World Report, published[5] "What to Know About the Latest COVID-19 Variant, HV.1".

HV.1 was responsible for about a quarter of new COVID-19 cases as of late October, rising to the highest prevalence of any strain circulating in the U.S.

HV.1 was documented by the CDC in low numbers over the summer.

But now the strain has the highest prevalence of any, claiming responsibility for about a quarter of new coronavirus cases in the U.S. as of late October.

HV.1 doesn't appear to cause more severe disease, but it is expected to bring the same high transmissibility that EG.5 has.

However, given how similar HV.1 is to EG.5, the updated coronavirus vaccines are expected to work on the new strain.

But the shot's advantages are limited by low uptake so far.

About 7% of U.S. adults and 2% of children got the new COVID-19 vaccines during the first month it was available, according to national surveydata.

COVID-19 weekly hospital admissions have been decreasing or stagnant for nearly two months, according to CDC data.

But the numbers remain elevated at more than 15,700 new admissions for the last full week in October, more than double summer's low of about 6,300 in June.

The CDC is predicting a "moderate" COVID-19 wave, according to its respiratory disease seasonoutlook.

"COVID-19 variants continue to emerge but have not resulted in rapid disease surges", the CDC said in an update to its respiratory disease season outlook published last month.

Experts expect that the group of variants circulating in the U.S. will continue to change as the virus spreads and adapts.

On November 15, The New York Times published the article for Dana G. Smith "What to Know About the New Covid Variants" highlighting that HV.1 has overtaken EG.5 as the leading variant in the U.S.[6]

The article short that two closely related variants, EG.5 and HV.1, as November 15, comprise roughly half of the COVID-19 cases in the United States with EG.5 became the dominant variant nationwide in August.

The World Health Organization classified EG.5 as a "Variant of Interest" on August 9, 2023, because the rise of EG.5.1, meaning it has genetic changes that give it an advantage and its prevalence was growing.

Since then, the variant appears to have plateaued, holding steady at about 20 to 25 percent of cases in September and October.

HV.1 emerged in the United States at the end of the summer and has progressively made up a larger proportion of the circulating virus.

According to the CDC, HV.1 overtook EG.5 as the dominant variant the week ending November 12, and now accounts for one in four COVID-19 cases.

Experts have also been watching two other variants, BA.2.86 and JN.1, that make up only a tiny fraction of cases but scientists say carry an alarming number of mutations.

While severe illness in older adults and people with underlying conditions is always a concern, as is long Covid in anyone who gets infected.

Experts say EG.5 and HV.1 do not pose a substantial threat, or at least no more of one than any of the other major variants that have circulated this year.

There isn't data yet on how well the new vaccines perform against HV.1.

Dr. Dan Barouch, the head of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center in Boston, said he doesn't anticipate it will be substantially different from their efficacy against EG.5.

Given the variants' similarity, it's unclear exactly how HV.1 has overtaken EG.5, but one of the few additional mutations in HV.1 has likely given it an edge over its predecessor.

"Whenever a new variant dominates, then by definition it has an advantage," Dr. Barouch said.

"And the advantage is either increased transmissibility or increased immune escape."

Another variant that scientists were watching closely earlier this fall was BA.2.86, nicknamed Pirola.

Experts were initially worried about this variant because of the number of mutations it carries in the spike protein, which is what the virus uses to infect human cells and what our immune systems use to identify it.

According to Jesse Bloom, a professor at the Fred Hutchinson Cancer Center who specializes in virus evolution, the mutations in BA.2.86 represent "an evolutionary jump similar in size" to the changes in the first Omicron variant compared to the original coronavirus strain.

Adding to the concern, early data indicated that the new vaccines may not be very effective against BA.2.86.

However,evidencehas since emerged that antibody levels produced in response to BA.2.86 are on par with those developed in response to EG.5, suggesting that the vaccines will be sufficiently protective against it.

A study posted September 5 in bioRxiv by Yunlong Cao from Biomedical Pioneering Innovation Center, Peking University, China, and colleagues, found that BA.2.86 may not be as transmissible as other forms of the virus[7].

Consequently, BA.2.86 has not taken hold like scientists worried it might; currently, there are no cases of it reported on the C.D.C. variant tracker.

Dr. Bloom said that it is not uncommon for new variants to fizzle out instead of spreading widely.

Just like EG.5 evolved to produce HV.1, JN.1 has recently emerged from BA.2.86.

According to data released October 18 on X (formerly Twitter) by Yunlong Cao and scientists in China, JN.1 carries a mutation that gives it extra immune-evading capabilities, but it doesn't appear to bind to human cells as well.

More than the risk conferred by any individual variant, it is the rapid rate of virus evolution that is most concerning to Trevor Bedford, a professor in the Vaccine and Infectious Disease division at the Fred Hutchinson Cancer Center.

"No single variant has been that impactful", he said, "but the overall accumulation of these mutations is having significant impact".

On November 26, Qian Wang and colleagues from Aaron Diamond AIDS Research Center, Columbia University, USA, published the article[8] "XBB.1.5 monovalent mRNA vaccine booster elicits robust neutralizing antibodies against emerging SARS-CoV-2 variants".

Pseudovirus neutralization assay, Phylogenetic analysis, and Antigenic cartography was performed.

Serum samples from 60 individuals across three different cohorts were collected.

The study showed that HV.1, HK.3, and JD.1.1 are more resistant to serum neutralization than XBB.15 by about 1.9-to-2.8-fold.

In the individuals vaccinated with the Pfizer XBB.1.5 Monovalent, HV.1 shows an ID_{50} close to 10^3, similar to HK.3, JD.1.1 and JN.1 SARS-CoV-2 variants.

In the individuals infected with the XBB.1.5 variant, HV.1 shows an ID_{50} close to 10^4, similar to HK.3, JD.1.1 and JN.1 SARS-CoV-2 variants.

In the individuals vaccinated with the Pfizer XBB.1.5 Monovalent, and previously infected with XBB.1.5, HV.1 shows an ID_{50} close to $10^{4.5}$, similar to HK.3, JD.1.1 and JN.1 SARS-CoV-2 variants.

On November 28, Bobbi-Jean Mackinnon, published in CBS News, New Brunswick, the article "2 new COVID-19 variants now dominant in New Brunswick".

HV.1 and HK.3, first detected in late August, have quickly overtaken other variants, data shows[9].

Two new COVID-19 variants quickly gaining traction across Canada are already dominant in New Brunswick.

So far, HV.1 and HK.3,related to Omicron EG.5, do not appear to cause more severe disease than other recent variants, said Colin Furness, an Infection Control Epidemiologistand Assistant Professor at the University of Toronto.

The volunteer groupProtect Our ProvinceNew Brunswick(PoP NB),which aims to create easy-to-access information on COVID risks and protection measures about HV.1 and HK.3 variant denote that:

"HV.1 and HK.3 were first detected in the province on New Brunswick in late August and represent about 15.7 per cent of confirmed cases sent for sequencingas of November 18".

Protect Our ProvinceNew Brunswick group obtained the data throughGISAID.

The provinceno longer providessequencing breakdownsin theRespiratory Watch report.

Public Health will only confirm the presence of a variantupon request, which Department of Health spokesperson Sean Hatchard said.

Three and a half years into the pandemic, "we still don't have a proper understanding of disease severity from variants with which we have lots of experience" said Collin Furness, Assistant Professor at the University of Toronto and infection control epidemiologist.

"Many of COVID's worst possible effects, vascular damage, brain damage, organ damage, will only be assessable in the long term", he said.

In addition, researchers know very little about what he described as the "plausible long-term effects", citing male infertility, accelerated dementia andcancer as examples.

"COVID-19 evolution appears to continue favouring (or selecting for) immune escape, but not contagiousness", Furness said.

"That benefits those who take active precautions to limit exposure, and it increases risk for those relying on immunity from past COVID-19 infections".

Since many people are not taking active precautions, he said, HV.1 and HK.3 are "finding a supportive environment".

HV.1 has grown dominant across Canada "very aggressively", while HK.3 is one of only about three

other subvariants that have increased even with HV.1 dominating, said Furness.

Theyare "theonly lineage groups demonstrating consistent growthacross the country", Health Canada noted in last week's epidemiology update.

As of November 12,HV.1 representsnearly 40 per centof sequenced cases nationally, while HK.3 accounts for nearly 12 per cent.

They have genetic changes that areknown to affect virus characteristics such as transmissibility and virulence; and a growth advantage over other circulating variants in more than one WHO region with increasingprevalence.

Although HV.1 and HK.3 have a high growth advantage relative to co-circulating variants,"their associated public health risks are classified lowat the global level", WHO said in its risk evaluation, published on November 21, 2023.

Department of Health spokesperson Sean Hatchard said in an email, thattheir presence in the province"does not at this time change the recommendations to New Brunswickers on how to protect themselves from COVID-19".

New Brunswickers are advised to "assess and manage their personal risk and to continue using Public Health precautions that can decrease their risk of contracting or spreading COVID-19", Hatchard said.

Henoted vaccination remainsthe best defence against COVID for those aged six months and older,as it "can help reduce the risk of serious complications and hospitalizations".

The province is scheduled to release the latest COVID update Tuesday afternoon.

As of the last Respiratory Watch report, covering November 5 to November 11,COVID-19 activity remained "moderate" and all indicators remained"stable".

On November 29, Lennart Schwenck from archide HomePanorama published "Understanding the HV.1 Corona Variant: Symptoms, Spread, and Impact", related to the rapid spread of the COVID-19 variant HV.1 in the USA is causing a stir[10].

Experts warn about the health effects.

The HV.1 SARS-CoV-2 variant continues to spread rapidly in the USA, and now dominates among new COVID-19 infections.

According to initial findings from experts, the new variant increasingly attacks the bronchi, the link between the lungs and trachea in our respiratory system.

Andrea Garcia, Vice President of the American Health Association (AMA), urged close monitoring of this new corona variant.

First detected in the summer of 2023, the HV.1 variant has replaced the previously dominant omicron subtype "Eris" (EG.5) in the USA.

Although the proportion of HV.1 variants among COVID-19 cases in the USA increased from 0.5 percent to 25.2 percent from July to November 2023, there are so far no reports of the spread of this variant in Germany.

The symptoms of HV.1 are similar to other omicron variants, making accurate identification difficult.

They are as follows: Stuffy nose, sore throat, runny nose, cough, exhaustion, headache, fever, chills, muscle pain if necessary, chronic bronchitis.

But what is particularly alarming is the suspected effect on the bronchi.

Dr. William Schaffnerfrom Vanderbilt University Medical Center told the US portalToday.com, that HV.1 could cause "a type of chronic bronchitis".

This is manifested by a persistent cough even after other symptoms have subsided.

Despite this worrying feature, there is currently no evidence that HV.1 is more contagious than other SARS-CoV-2 variants.

In Germany, the omicron subvariants Eris, Pirola and JN.1 continue to dominate the list of new infections.

Although no cases of HV.1 have been detected so far, the Robert Koch Institute has recorded a significant increase in the overall number of infections.

Unreported cases in Germanyhowever, it is likely to be higher due to people not being tested.

Possible infections can be counteracted with preventive measures such as regular hand washing.

If you suspect an outbreak of infection, it is advisable to do a rapid COVID-19 test.

These are available in most pharmacies or drugstores.

Meanwhile, reports of a wave of infections in China, which primarily affects children, also caused excitement.

On November 30, the COVID-19 Real-Time Learning Network, published[11] "Will New COVID Vaccines Work Against EG.5 and HV.1?", and quote:

Q: What are the EG.5 and HV.1 variants?

a. EG.5 and HV.1 are SARS-CoV-2 Omicron variants that currently make up more than half of SARS-CoV-2 cases in the U.S. (CDC November 2023).
b. HV.1 is currently growingin the U.S. and is descended from EG.5.
c. The two variants are genetically similar, and both stem from the XBB Omicron lineage.

Q: Do the EG.5 or HV.1 variants cause more severe disease than other Omicron variants? Are they more transmissible than other variants?

a. At present, it does not appear that EG.5 or HV.1 cause more severe disease than other Omicron variants, nor do they appear to be substantially more transmissible than other Omicron variants.
b. Despite there not being clear genetic changes that are associated with increased transmissibility, it appears that EG.5 has a growth advantage over other Omicron lineages.
c. This may be due primarily to the fact that it is new and replicating in an environment where many individuals do not yet have antibodies capable of neutralizing these variants.
d. Preliminary evidence suggests that EG.5.1 does evade antibody-mediated immune protection to a moderate extent (Faraone, October 2023;Kaku, August 2023).

Q: Do vaccines protect against EG.5 and HV.1 variants?

a. Yes. Updated SARS-CoV-2 vaccines contain antigens against an XBB variant that seems to produce antibodies capable of neutralizing EG.5.
b. Information on vaccine-mediated neutralizing capacity against HV.1 is still being investigated, but it is expected that it will be similar to that of EG.5 due to the variants genetic similarity.
c. Despite the capability of updated vaccines to produce antibodies capable of neutralizing these variants, the rapid development of both EG.5 and HV.1 do indicate the need for continued epidemiologic surveillance and COVID-19 vaccine updates.

Q. Do other therapeutics protect against EG.5 and HV.1?

a. Yes.Therapeutics, such as Paxlovid, are still expected to offer protection by reducing the severity of infection from either variant.

Q: Are tests still capable of identifying SARS-CoV-2 infections caused by EG.5 or HV.1?

a. Yes. Although still being gathered, information about the genetic features of these viruses suggests that PCR tests and at-home antigen tests will still be able to identify SARS-CoV-2 infections caused by these variants (Faraone, October 2023;Abbasi, September 2023).

On December 1st, CDC in the "Weekly Viral Respiratory Illness Snapshot" report, provides a summary of the key viral respiratory illness findings for COVID-19, influenza, and RSV from the week ending November 26, and access to additional information and figures[12].

The amount of respiratory illness (fever plus cough or sore throat) causing people to seek healthcare is increasing across most areas of the country.

The U.S. is experiencing elevated RSV activity, particularly among young children.

After a period of limited change, COVID-19 activity is increasing again especially in the Midwest and Mid-Atlantic regions.

Influenza activity continues to increase in most of the country.

Hospital bed occupancy for all patients, including within intensive care units, remains stable nationally; however, pediatric inpatient bed occupancy has been increasing.

Vaccines are available andcan help protectpeoplefrom the most serious health effects of fall and winter viruses.

COVID-19 test positivity (percentage of tests conducted that were positive), emergency

department visits, and hospitalizations have increased nationally.

A group of Omicron variants (XBB and its sublineages) are the predominant lineages detected in the U.S., with HV.1 being most common.

The prevalence of another lineage, BA.2.86, is projected to account for 5-15% of currently circulating variants.

The Centers for Disease Control and Prevention continues tomonitorHV.1, BA.2.86, and all other lineages.

National test positivity, emergency department visits, and hospitalizations for influenza continue to increase.

RSV emergency department visits and hospitalizations continue to increase across the country.

RSV-associated hospitalization rates remain elevated among young children and are increasing among older adults; of note, only 14.8% of adults 60+ report having received an RSV vaccine.

National vaccination coverage for COVID-19, influenza, and RSV vaccines increased less than one percentage point for children and adults, where indicated, compared to the week ending November 26, and remains low for both groups.

Increases in respiratory illness reported recently among children, including potential elevated rates of pediatric pneumonia in parts of the United States, CDC has been monitoring.

These reported increases do not appear to be due to a new virus or other pathogen but to several viral or bacterial causes that we expect to see during the respiratory illness season.

On December 6, The American Medical Association -AMA- published[13] "CDC updates on the latest COVID variants, flu and RSV in kids, plus pneumonia outbreak in China".

American Medical Association Vice President of Science, Medicine and Public Health, Andrea Garcia, breaks down the latest vaccine news including why now is still a great time to get the flu vaccine and how your mood could impact how effective the flu vaccine is.

She also discuss the latest rise in COVID-19 cases and the particularly hard impact COVID-19 and RSV are having on children this year.

She remarks that the variant AMA discussed last week, BA.2.86, is continuing to make headlines, and that's because it increased almost triple-fold over a two-week period.

It's responsible for about 1 in 10 COVID-19 cases right now.

HV.1 is still the most prevalent SARS-CoV-2 variant in the U.S., and it's making up about 31.7% of cases.

Right now, all indicators are pointing to rising COVID-19 numbers.

And, as we've discussed before, wastewater tracking is one of those early indicators that health officials increasingly rely on to gauge that activity of SARS-CoV-2 and other viruses.

On December 6, Lydia Stephens Health editor of Wales Online News, Health, Coronavirus, published[14] "Coronavirus symptoms December 2023 as cases of virus expected to rise over Christmas period".

In brief, the experts believe cases of coronavirus will rise over the next few weeks as more people mingle through theChristmasperiod.

Coronavirusand other seasonal illnesses like colds and flu tend to peak over the winter months.

A new coronavirus variant has been identified by scientists and could make people ill over Christmas, includes JN.1 and HV.1.

The new strain, Pirola JN.1, was found in Luxembourg in August and has spread to the U.K., U.S., France and other countries.

A specific mutation in JN.1 makes it more infectious, according to researchers.

Professor Sheena Cruickshank, immunologist at the University of Manchester, said that it could take longer to recover from or cause more severe disease.

She said: "One of the mutations JN.1 seems to have is the potential to help it better latch onto cells, making it better at infecting us.

That, coupled with immune evasion mechanisms, mean it may be tricky for our immune systems to get rid of".

Professor Cruickshank said that "by inference" this should also mean vaccines work well against JN.1.

However, there has been a low uptake in both the coronavirus and flu vaccines in Wales this year.

According to theWelsh Government, just over a third of all those eligible have had theircoronavirusbooster vaccine this season.

Wales top doctor has warned that it is "vital" for those most at risk of winter illnesses to take up the offer of a coronavirusand or flu vaccination when they are invited.

Reported a list of symptoms for HV.1 that include Fever, Coughing, Tiredness, Nasal Congestion and Runny nose.

On December 6, David Ho from Columbia University, and colleagues, published in bioRxiv[15] new results of the paper "XBB.1.5 monovalent mRNA vaccine booster elicits robust neutralizing antibodies against emerging SARS-CoV-2 variants".

The Abstract resume that COVID-19 vaccines have recently been updated with the spike protein of SARS-Co-V-2 XBB.1.5 subvariant alone.
Their immunogenicity in humans has yet to be fully evaluated and reported, particularly against emergent viruses that are rapidly expanding.
They report that administration of an updated monovalent mRNA vaccine (XBB.1.5 MV) to uninfected individuals boosted serum virus-neutralization antibodies significantly.
Works against not only XBB.1.5 (27.0-fold) and the currently dominant EG.5.1 (27.6-fold) but also key emergent viruses like HV.1, HK.3, JD.1.1, and JN.1 (13.3-to-27.4-fold).
In individuals previously infected by an Omicron subvariant, serum neutralizing titers were boosted to highest levels (1,764 to 22,978) against all viral variants tested.
While immunological imprinting was still evident with the updated vaccines, it was not nearly as severe as the previously authorized bivalent BA.5 vaccine.
Our findings strongly support the official recommendation to widely apply the updated COVID-19 vaccines to further protect the public.

On December 7, The Jakarta Post from Indonesia, published[16] "Indonesia calls for public vigilance over emerging COVID subvariants".

In Jakarta, the Health Ministry has urged greater vigilance amid a recent uptick in cases of new COVID-19 subvariants, both in the country and around the globe, while reassuring the public on the availability of vaccines.

Health Ministry spokesperson Siti Nadia Tarmizi told The Jakarta Post on Tuesday that a the number of novel coronavirus infections had risen "from previously only 10 to 20 cases weekly to 276 cases last week".
EG.5, informally dubbed "Eris", and EG.2 had become the dominant Omicron subvariants in Indonesia, but did not say how many confirmed cases had been linked to these subvariants.
In August, the World Health Organization classified the Omicron subvariant EG.5 and its sublineages HK.3 and HV.1 as variants of interest (VOIs).

A VOI is less serious than a variant of concern (VOC) on the United Nations health agency's classification system.

Generally, reflects a subvariant's relative prevalence compared to others circulating in an area or region and its potential epidemiological changes "to suggest an emerging risk to global public health". The World Health Organization said there was no evidence so far that EG.5 caused more severe symptoms, but noted that more comprehensive risk evaluation on emerging EG.5 sublineages like HK.3 and HV.1 was needed.

Siti advised people who were not feeling well as well as the elderly to wear masks, and that anyone with symptoms should see a doctor or other health worker. She also emphasized that the country had a sufficient supply of vaccines and encouraged everyone to complete their two-dose vaccination against COVID-19.
The ministry also urged people "to postpone traveling to countries currently experiencing a surge in COVID-19 cases".

Singaporean health authorities advised vigilance after the island state saw the number of estimated COVID-19 infections double to some 22,000 in the week from November 19 to 25, compared to an estimated 10,700 cases the week prior. EG.5 and its sublineage HK.3 made up around 70 percent of the cases that were sequenced. Malaysia recorded a 57 percent increase in its weekly caseload during the final week of November, from some 2,300

cases the previous week, with the majority of cases experiencing only mild symptoms.

Though it was unclear if EG.5 had been detected in the neighboring country, it recorded two cases of BA.2.86, another new Omicron subvariant classified as a VOI.

Indonesia detected its first EG.5 infection in June, the same month that President Joko Widodo lifted the COVID-19 health emergency status and all remaining health restrictions that had been in place for more than three years.

On December 11, HindustanTimes published the article by Jahanvi Sharma[17] "All about leading COVID-19 variants HV.1, EG.5 and others spreading wings across US".

Four new variants of COVID-19 namely, HV.1, EG.5, BA.2.86 and JN.1 are being tracked by scientists in the US.

EG.5 and HV.1, two closely related variants, currently comprise nearly half of the COVID-19 cases in the US.

EG.5 became the dominant variant in August.

At the time, WHO classified it as a "Variant of Interest," meaning its genetic changes gave it an advantage and its prevalence within the country was growing.

In September, it peaked with about 25% of cases and has now declined to 13% in December.

HV.1 emerged at the end of summer 2023 and has made quite a progress to a larger proportion of the spreading virus.

As per the CDC, it overtook EG.5 as the dominant variant in late October and now accounts for over 30% of the cases.

The other two variants being tracked by scientists are BA.2.86 and JN.1, which they say are carrying an alarming number of mutations.

They together make up the 9% of cases in the US and are on the rise.

According to experts, EG.5 and HV.1 SARS-CoV-2 variants don't pose a substantial threat as compared to the other variants that peaked this year.

Given the variants likeness, it's unclear exactly how HV.1 has overtaken EG.5, but one of the few additional mutations in HV.1 has likely given it an edge over its predecessor.

On December 13, TWC India Edit Team from The Weather Channel India, Coronavirus, published[18] "Four New COVID-19 Variants Are Raising Concerns in the US. Here's All About Them".

While both EG.5 and HV.1 are currently found in nearly half of all COVID-19 cases in the US, experts note that these do not pose a major threat compared to other variants.

EG.5 initially peaked at 25% of total record US COVID-19 cases in September, but has since declined to 13% in December.

HV.1, on the other hand, rapidly rose to prominence after emerging in late summer and now accounts for over 30% of cases in the country.

New vaccines that counter XBB also appear to work against both these strains.

Added that JN.1 sub-variant was recently detected in Kerala for the first time, the latest data from the Indian SARS-CoV-2 Genomics Consortium (INSACOG) showed.

The emergence of these new variant underscores the constant evolution of the COVID-19-causing novel coronavirus.

Continued vigilance and monitoring are crucial in staying ahead of the curve.

While existing vaccines remain our primary defence, researchers are actively developing updated versions to tackle new threats like JN.1.

Individual precautions like masking, social distancing and staying up-to-date on vaccinations continue to be essential in protecting ourselves and our communities.

By staying informed and taking necessary measures, we can navigate this evolving landscape and emerge stronger from the pandemic.

On December 13, The World Health Organization in the "News/Statement on the antigen composition of COVID-19 vaccines" published[19]:

The TAG-CO-VAC reconvened on 4-5 December 2023 to review the genetic and antigenic evolution of SARS-CoV-2, the performance of currently

approved vaccines against circulating SARS-CoV-2 variants, and the implications for COVID-19 vaccine antigen composition.

The twice-yearly evidence review by the TAG-CO-VAC is based on the need for continued monitoring of the evolution of SARS-CoV-2 and the kinetics of vaccine-derived immunity.

The evidence reviewed include the published and unpublished evidence reviewed by the TAG-CO-VAC included:

(1) SARS-CoV-2 evolution, including genetic and antigenic characteristics of earlier and current SARS-CoV-2 variants, and the impact of SARS-CoV-2 evolution on cross-neutralization and cross-protection following vaccination and/or infection;
(2) Vaccine effectiveness (VE) of currently approved vaccines during periods of XBB descendent lineage circulation;
(3) Antigenic cartography analyzing antigenic relationships of SARS-CoV-2 variants using naïve animal sera and human sera following vaccination and/or infection;
(4) Preliminary immunogenicity data on the performance of currently approved vaccines against circulating SARS-CoV-2 variants using animal and human sera; and
(5) Cellular (T and B cell) immune responses following vaccination and/or infection. Further details on the publicly available data reviewed by the TAG-CO-VAC can be found in the accompanying data annex. Unpublished and/or confidential data reviewed by the TAG-CO-VAC are not shown.

Regarding hv.1 summarizes:

- Several of these XBB- and BA.2.86 derived variants (e.g., EG.5, HV.1, HK.3, JN.1) have independently-evolved changes in the spike protein at a neutralizing antibody epitope involving amino acid residues 455 and/or 456. This highlights the current immune pressure on this epitope.
- In naïve animals, monovalent XBB.1.5 vaccines elicited neutralizing antibodies that cross-reacted well with XBB descendent lineages (e.g., EG.5, HV.1, HK.3). However, BA.2.86 and JN.1 were not neutralized well, indicating that BA.2.86 and JN.1 are antigenically distinguishable from XBB.1.5 in this model.
- In contrast, sera from humans vaccinated with XBB.1.5 monovalent vaccines, with or without recent prior infection, neutralized XBB descendent lineages including EG.5, HK.3, HV.1, as well as BA.2.86 and JN.1. However, there are only limited data on cross neutralization of JN.1.

On December 13, Annu Mandal from FE Health Care/Business News/Healthcare/Covid 19/Covid Variant Alert! US, published[20] "Reports 3 New Strain Of Coronavirus; all You Need To Know About HV.1, EG.5, BA.2.86 Variants".

The COVID-19 pandemic that shook the world doesn't seem to end soon when some US scientists discovered four more variants of the virus recently namely, HV.1, EG.5, BA.2.86 and JN.1.

The number of cases has been really low comparatively with the help of the vaccine but these vaccines are not enough to tackle all, as per reports.

Researchers have found that EG.5 and HV.1 are two closely related variants that are persistent in half of the COVID victims.

EG. 5 peaked at around 25% in September and has since dropped to 13% in December.

HV.1 emerged at the end of summer and became the dominant variant in late October and now accounts for more than 30% of cases.

On the other hand, BA.2.86 and JN.1 carry an alarming number of mutations as they together make up 9% of cases in the US and consistently rising.

According to experts, the EG.5 and HV.1 variants, though present, do not pose a significant threat compared to other variants that were prominent this year.

The exact reason for HV.1 overtaking EG.5 is not entirely clear, but one of the few additional mutations in HV.1 likely gives it a competitive edge over EG.5.

Despite these developments, experts maintain that these variants do not pose a substantial threat compared to other variants that were more prominent during the course of the year.

A new variant, JN.1, has emerged from BA.2.86 and is spreading rapidly.

It possesses a L455S mutation that provides it with additional immune-evading capabilities.

While preprint paper results testing the new vaccines against HV.1 showed effective antibodies against JN.1, the levels are not as high.

This raises some concerns about the effectiveness of the vaccines against JN.1, despite their protective abilities against other variants.

County of Los Angeles, Public Health, published on December 14, 2023[21], "As COVID-19 Transmission Indicators Increase, Common-Sense Precautions offer Important Protection from Exposures, Transmission and Severe Illness".

Three weeks after Thanksgiving, Los Angeles County is seeing an increase in indicators of COVID-19 transmission.

With cases rising, new variant strains emerging, and the ongoing risk of Long COVID, residents may want to consider taking common sense precautions to limit exposures, transmission and severe illness.

This includes wearing a high-filtration mask in high-risk situations, testing when symptomatic, remaining home when sick, and importantly, getting the updated COVID-19 vaccine soon.

In Los Angeles County, the proportion of cases that different strains account for has shifted over recent weeks, signaling that COVID-19 is continuing to evolve with new strains gaining dominance.

The updated vaccine is formulated to provide protection for Omicron XBB strains, which are circulating now.

Currently, in Los Angeles County, for specimens collected the two-week period ending November 11, strains descended from XBB accounted for 95 percent of sequenced specimens.

HV.1 accounted for the highest proportion, at 27 percent, followed by EG.5 at 18 percent.

As a comparison, for specimens collected during the same period in 2022, less than 5 percent of specimens were descendants of Omicron XBB.

In many cases, the strains that were dominant when a person was vaccinated or infected in the past may no longer be widely circulating.

The updated vaccine can renew protection against severe illness and hospitalization and ensure a person has the most needed protection this winter.

Since early November, COVID-19 hospitalizations in Los Angeles County have been steadily increasing.

For the most recent week, based on data through December 2, the CDC is reporting 6.3 new COVID-19 hospitalizations per 100,000 people, compared to 4.8 the week prior.

The daily average of the percent of Emergency Department encounters classified as coronavirus-related is 4 percent compared to 3 percent one month ago.

On December 15, Ashleigh Hollowell from Beckers Healthcare published the note[22] "COVID hospital admissions up 3%".

As COVID-19-related hospital admissions haverisenfor another week in a row, 23,432 in the most recently reported week, the CDC is alsoalertingclinicians tolow vaccination rates, urging them to emphasize its importance in preventing severe infection.

Right now, uptake of the latest COVID-19 vaccine stands at 17% in adults, and 7.7% in children 6 months to 17 years old.

Five more updates:

- The latest variant, JD.1, nowaccounts for21.4% of COVID-19 cases in the U.S., which the CDC says could mean it is "either more transmissible or better at evading our immune systems."
- However, theleading variantmaking up the highest percentage of COVID-19 cases currently is HV.1.
- Nine states are currently reporting moderate levels of COVID-19 activity, including: Montana, Wyoming, South Dakota, Nebraska, Iowa, Missouri, Indiana, Kentucky and West Virginia.
- Kentucky has had the most COVID-19 deaths in recent weeks, up 108% from the week prior.
- Nationally, deaths due to COVID-19 as of Dec. 9 showed little change.

On December 15, Sijie Yang from NUSUrban Analytics Lab at National University of Singapore and colleagues published in The Lancet the article[23] "Fast evolution of SARS-CoV-2 BA.2.86 to JN.1 under heavy immune pressure".

About HV.1 variant remarks:

- JN.1's plasma evasion surpassed that of competitive variants HV.1 (EG.5+L452R) and JD.1.1 (FLip+A475V).

- HV.1 and JD.1.1 also showed significantly lower plasma neutralisation titers compared with their parental strains after acquiring L452R and A475V mutations, respectively, explaining their growth advantages.
- A475V mutation carried by JD.1.1 (XBB.1.5+FLip+A475V) also resulted in decreased binding affinity, enhancing immune evasion compared to HK.3 (XBB.1.5+FLip).
- However, the L452R mutation of HV.1 did not affect binding affinity.

In summary, JN.1, by inheriting BA.2.86's antigenic diversity and acquisition of L455S, rapidly achieved extensive resistance across receptor binding domain class 1, 2, and 3 antibodies.

Showed higher immune evasion compared with BA.2.86 and other resistant strains like HV.1 and JD.1·1, at the expense of reduced human ACE2 binding.

On December 18, the TrialSiteNews published the article by the journalist Maryam Md[24] "The Omicron Family Gets Bigger: Characteristics of New Dominant Subvariant HV.1".

According to CDC, the second half of the November 2023 data demonstrates that the HV.1 subvariant of the SARS-CoV-2 virus comprises 31.7% of all cases in the U.S.

This makes it the new dominant subvariant circulating in the U.S. sincemid-August.

The Omicron family in general is highlytransmissible,and HV.1 is no exception which makes it a concern for public health.

Infectious disease professor atVanderbilt University Medical Center,William Schaffner, M.D.stated that while HV.1may be more transmissible, it does not appear to cause more severe disease or hospitalizations.

"I don't think people should be very concerned about this", he said.

On the other hand, Schaffner alsowarnsabout the possible increase of cases in winter, as was the case for the past three years.

The symptoms of the HV.1 are not different from classicalCOVID-19 symptoms, including fever, cough, fatigue and sore throat.

No new or alarming symptoms have been observed with the emergence of HV.1.

The severity of these symptoms can vary depending on an individual's immunity and vaccination status.

Additionally, while these symptoms are mostly mild, they can be dangerous for immunocompromised individuals.

Unlike its family members, HV.1 still does not have a catchy nickname, so all the sources still use the scientificPango name.

Healthcare professionals continue to investigate this new variant, and fortunately, most diagnostic tests currently in use can still reliably diagnose the various strains of the SARS-CoV-2 virus.

Mutations that cause HV.1 allow it to infect people with previous immunity to the SARS-CoV-2 virus more easily.

Therefore, it is an important concern if the vaccines and other preventive and therapeutic measures can keep up with these new subvariants.

Modernaannouncedin August 2023 that its updated COVID-19 vaccine will target the expected circulating variants of COVID-19.

The president of Moderna,Stephen Hoge, specifically claimed that the new results from the clinical trial data of the updated COVID-19 vaccine illustrated a robust immune response against the XBB strains including the EG.5 subvariant.

Pfizer also created a version of its shots to target the XBB strain, andReutersmentionedthat it showed effectiveness against EG.5 in a mice study.

Although they did not specifically state HV.1, since it is from the same family as XBB, one canassumethat updated vaccines are expected to be effective against this new dominant subvariant.

Matthew J. Binnicker, who studies viral infections and is a Director of Clinical Virology atMayo Clinic, emphasized that along with the updated vaccines, antiviral treatments such as Paxlovid can still work for the HV.1.

For now, the dominant variant HV.1 does not seem harmful in terms of creating a deadly disease but is still contagious enough to not be ignored.

On December 19, Arya Vaishnavi from the Hindustan Times published the article "New Covid variant HV.1 is spreading across US states, here are its symptoms" and states[25]:

A newCOVID variant called HV.1has been spreading across US states. It is a highly contagious omicron subvariant, which was first reported in the late summer.

According to the US Centers for Disease Control and Prevention, it rapidly overtook other COVID-19 variants, which includes EG.5, back in October.

In December, it accounted for 30 per cent ofnew COVID-19 infectionsamong US citizens.

The CDC added that often mutations enable new variants to spread more rapidly.

While the list is not exhaustive, similar to other variants the symptoms of HV.1 include:

1. Fever or chills
2. Cough
3. Shortness of breath or difficulty breathing
4. Fatigue
5. Muscle or body aches
6. Headache
7. New loss of taste or smell
8. Sore throat
9. Congestion or runny nose
10. Nausea or vomiting
11. Diarrhea

William Schaffner, M.D., an infectious disease specialist and professor at the Vanderbilt University School of Medicine said:

"You can almost think of HV.1 as a grandchild of omicron".

"The COVID family of viruses likes to mutate. We've all learned that by now," according to Today.

"One of the characteristics of this entire omicron family is that they are highly transmissible".

"Congestion, sore throat and dry cough seem to be the three most prominent symptoms right now", Schaffner continued.

"The virus seems to produce a kind of a chronic bronchitis, so that you can have a cough syndrome that lasts beyond the period where you've recovered from other symptoms".

"The only way to distinguish (COVID-19) from RSV and flu, both of which are now gaining steam, is by testing" remarks.

On December 20, Kath Katella from Yale Medicine, published[26] "JN.1 and Other New Coronavirus Variants: 3 Things to Know", and about HV.1 brief:

As cold winter weather drives people indoors and flu, colds, and other seasonal respiratory viruses circulate, SARS-CoV-2 has continued to mutate and spread.

The latest strain to attract attention is called JN.1, and so far, it appears to be highly transmissible.

There are other variants, too, including HV.1, which in early December was the dominant strain in the United States, causing over 29% of cases, more than any other variant.

EG.5, which had been the dominant strain since the summer, dropped to second place in November and, by mid-December, accounted for less than 10% of cases.

Katella remarks about the increased prevalence of JN.1:

The JN.1 strain surfaced in the U.S. in September.

It is a close relative of BA.2.86 variant that the CDC has been tracking since August.

While the Omicron variant, which first took hold in the U.S. in 2021, has had multiple descendants, the original strain is no longer in circulation.

A difference between BA.2.86 and JN.1 is that the latter has L455S mutation in its spike protein.

This single change that may or may not alter any of the traits that characterize the virus, althoughpreliminary researchshows that it may provide extra immune evasion.

On December 22, Caroline Kee, from TODAY, Coronavirus, published[27] "COVID variant, HV.1, is still spreading. These are its most common symptoms".

As winter officially begins in the United States, COVID-19 is on the rise around the country.

Multiple variants of the virus are driving infections, but two strains, HV.1 and JN.1, account for the majority of cases nationwide.

HV.1, a highly contagious subvariant of omicron, is currently responsible for an estimated one-fifth of cases in the U.S.

The HV.1 variant has been circulating in the U.S. since the late summer.

In October, HV.1 quickly overtook other strains, includingEG.5, to become the leading variant in the country, according tothe CDC.

HV.1 remained the dominant strain until mid-December, when it was overtaken by JN.1, which is an offshoot ofBA.2.86 or Pirola.

During a two-week period ending on Dec. 23, JN.1 accounted for an estimated 44% of COVID-19 cases, followed by HV.1, which made up about 22% of cases, per the latest CDC data.

All of the COVID-19 variants that have become dominant in the U.S. during the last year aredescendants of omicron, which began circulating in November 2021.

HV.1 descended from EG.5, and is highly similar to its parental strain.

The emergence of HV.1 demonstrates how the SARS-CoV-2 virus, which causes COVID-19, is able to mutate and give rise to new, highly contagious variants.

Experts say theupdated COVID-19 vaccinesrolled out in September still offer protection against newer strains, including HV.1 and JN.1, but uptake has been low so far.

“You can almost think of HV.1 as a grandchild of Omicron,” says William Schaffner from the National Foundation for Infectious Diseases.

While HV.1 is mutated, it's still very close to the existing omicron subvariants, Schaffner explains.

For the most part, scientists are not concerned about new variants like HV.1, which look very similar to strains we've already seen before,NBC News reported.

However, there are a few highly mutated strains that have set off alarm bells in the past.

These includeBA.2.86 or Pirola, which has an extra 36 mutations that differentiate it from XBB.1.5, and a new fast-growing variant called JN.1.

JN.1 is a direct descendent of Pirola with one additional mutation, and it has quickly gained speed in recent weeks, overtaking BA.2.86.

However, there's no evidence that JN.1 is more severe and it does not present an increased public health risk, the CDC said in an update published on December 8.

In late July, HV.1 accounted for just 0.5% of COVID-19 cases in the U.S.,CDC data show.

By September 30, HV.1 made up 12.5% of cases, and by November, it was the dominant strain.

Right now, it appears that HV.1 could be better at spreading from person to person than previous strains, NBC News reported.

The increased transmissibility of HV.1 likely explains how it became dominant so quickly in the U.S., Schaffner notes.

It also appears that HV.1 could also be slightly better at escaping prior immunity to COVID-19, but not enough to cause alarm, Dr. Dan Barouch, director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center in Boston, told NBC News.

"The problem is that most people's immunity has faded from past outbreaks and our vaccine uptake is still very low, it's too soon to draw any conclusions about HV.1 evading immunity from prior infection or vaccination" says the Epidemiologist Pyria Sampathkumar.

Although it is more transmissible, HV.1 does not appear to produce more severe disease or lead to more hospitalizations, Schaffer says.

The recent increase in COVID-19 activity is expected because it has had a pattern of peaking around the late summer and again around the New Year,the CDC said.

What remains unclear is whether HV.1 could cause a major surge in COVID-19 cases in the coming weeks.

"If there's vast numbers of people getting infected, even if the disease for most people isn't very severe, we will see an uptick in hospitalizations and deaths," says Sampathkumar.

Health officials are monitoring HV.1 closely, but low levels of testing have made it harder to accurately track new variants, experts note.

The symptoms caused by infection with HV.1 are similar to those caused by recent variants, says Schaffner, which include:

- Sore throat
- Congestion or stuffiness
- Runny nose
- Cough
- Fatigue
- Headache
- Muscle aches
- Fever or chills

“Congestion, sore throat and dry cough seem to be the three most prominent symptoms right now,” says Schaffner.

Increasingly, doctors report that COVID-19 symptoms appear to follow a pattern of being concentrated in the upper respiratory tract, starting with a sore throat and followed by congestion or a runny nose, NBC news reported.

Coughing isn't typically a primary symptom, but it can persist.

"The virus seems to produce a kind of a chronic bronchitis, so that you can have a cough syndrome that lasts beyond the period where you've recovered from other symptoms," says Schaffner.

"I haven't really heard of anything very different or any new symptoms that may raise alarms," says Sampathkumar.

Another trend is that COVID-19 seems to be causing milder illness, likely because people have some prior immunity.

“By milder, we mean it doesn't require hospitalization even though you can feel quite miserable for several days,” says Schaffner.

All COVID-19 tests, including PCR tests performed by a health care provider and rapid at-home antigen tests, will detect HV.1, says Schaffner.

Testing is a crucial tool to protect yourself and others from COVID-19.

The symptoms of HV.1 and other COVID-19 variants can look very similar to other viruses, including respiratory syncytial virus (RSV), influenza and rhinovirus, which usually causesthe common cold.

There's no way to tell these viruses apart based on symptoms alone, says Sampathkumar.

"The only way to distinguish (COVID-19) from RSV and flu, both of which are now gaining steam, is by testing," says Schaffner.

Experts encourage anyone who has symptoms or has been exposed to get tested, especially those in high-risk groups, people over the age of 65, who are immunocompromised or who have underlying health conditions.

“We have treatments that can prevent more serious disease," says Schaffner, but early detection is key.

COVID-19 antivirals such asPaxlovidare effective against HV.1 and other variants, but they work best when within five days of symptom onset, TODAY.com previously reported.

Testing has significantly diminished in the U.S. in the last year, which is concerning, says Schaffner.

When the U.S. federal publichealth emergency for COVID-19 endedin May, so did the guarantee of free testing for many.

Now, the cost of COVID-19 testing will vary depending on your health insurance plan.

However, every American can stillorder four free at-home COVID-19 testsfrom the government, which will be delivered by mail via the U.S. Postal Service.

Uninsured individuals may still be able to access free or low-cost tests through community health centers and participating pharmacies, perHealth & Human Services.

If you still have a stockpile of tests sitting around, remember to check the expiration date and whether it's been extended bythe U.S. Food and Drug Administration.

Theupdated COVID-19 vaccineis recommended by the CDC for everyone ages 6 months and older.

It is now widely available at pharmacies, doctor's offices and other locations around the U.S., says Schaffner.

The new boosters have been reformulated to target omicron XBB.1.5, which was the dominant COVID variant for most of 2023.

While XBB.1.5 has since been overtaken by HV.1 and other variants, it is still closely related to these newer strains.

The updated shots seem to be well-matched to the variants currently circulating and making people sick, Andrew Pekosz, virologist at Johns Hopkins University, previously told TODAY.com.

"Laboratory studies indicate that the updated booster will protect against serious disease caused by HV.1," says Schaffner.

Vaccination also significantly lowers the risk of becoming hospitalized or dying,per the CDC.

As of December 15, only about 18% of adults and 8% of children in the U.S. have gotten the new vaccine, according to thelatest CDC data on vaccination trends.

The first phase of the vaccine rollout hit several speed bumps, including supply delays, cancelled appointments and insurance obstacles.

Some parents were unable to get theirkids vaccinatedearly on, as some pharmacies and pediatrician's offices have struggled to secure enough child-size doses.

Although many of these initial issues have been resolved, says Schaffner, uptake is still slow.

"We've underutilized this updated vaccine, and we anticipate that COVID will once again increase even more during the winter season," says Schaffner.

It's not too late to take advantage of the new booster, Schaffner adds, and people should get the shot as soon as they can.

While people are getting their COVID-19 vaccine, they should get their seasonal flu shot as well, Sampathkumar adds.

The FDA has authorized three vaccine options for 2023-2024: one mRNA shot each from Moderna and Pfizer, and a protein-based non-mRNA shot from Novavax.

Insurance plans should cover the updated booster, says Schaffner, and those without insurance should still be able to get the shot for free,according to the CDC.

"We're in a good place because for a considerable time now, we have not had a new variant that causes more severe disease or evades the protection of currently available vaccines," says Schaffner.

Some missense mutations alter the function of the resulting protein (NIH National Human Genome Research Institute, updated December 19, 2023)[28].

AMissense Mutationis a DNA change that results in different amino acids being encoded at a particular position in the resulting protein.

On December 22, Public Health Ontario published the Surveillance Report[29] "Integrated Respiratory Virus Risk Indicators for Ontario: December 17, 2023, to December 30, 2023".

The report provides short-term projections of SARS-CoV-2, influenza, and respiratory syncytial virus (RSV).

The activity and risk of related severe viral respiratory disease (i.e., hospitalizations related to the three viruses) in the pediatric (<18 years) and general adult (18-64 years) populations in Ontario is included.

The "nowcast" estimation methodology1 used to create these indicators relies on data reported up to December 16, 2023.

The report highlights[30]: Over the next two weeks, the following changes are projected for SARS-CoV-2, influenza, and RSV activity in Ontario:

- SARS-CoV-2 activity is projected to decrease.
- Influenza activity is projected to increase.
- RSV activity is projected to decrease.
- The risk of related severe respiratory virus illness for the most recent week of available data is very high in the pediatric population and in the general adult population.
- The risk of severe illness among the pediatric population is projected to decrease.
- The risk of severe illness among the general adult population is projected to increase.

The latest report from SARS-CoV-2 Genomic Surveillance in Ontario, Canada, December 18, 2023, published on December 19, 2023, shows the number of COVID-19 cases, number and percentage of cases sequenced for representative surveillance by week, November 5 to December 2, 2023[31].

- In the most recent week (November 26 to December 2), a total of 2,096 cases were sequenced. HV.1 was the most prevalent lineage (36.4%), followed by JN.1 (11.1%), and JG.3 (7.7%).
- The proportion of HV.1 remained stable at 36.5% (November 19 to November 25) and 36.4% (November 26 to December 2).

- Based on the Nowcast model, HV.1 is projected to decrease to 24.0% (95% CI: 20.7% - 27.7%) by December 20, 2023.
- The proportion of JN.1 increased from 6.5% (November 19 to November 25) to 11.1% (November 26 to December 2).
- Based on the Nowcast model, JN.1 is projected to increase to 40.5% (95% CI: 33.4% - 48.1%) by December 20, 2023.
- The weekly growth rate of JN.1 is 1.78 (95% CI: 1.66 - 1.92) times that of HV.1.

The Table shows the Number of COVID-19 cases, number and percentage of cases sequenced for representative surveillance by week, Ontario, November 5 to December 2, 2023.

Week	Number of cases	Number sequenced	Percentage sequenced
Week 45 (November 5 - November 11)	3,547	2,117	59.7%
Week 46 (November 12 - November 18)	4,305	2,342	54.4%
Week 47 (November 19 - November 25)	4,488	2,649	59.0%
Week 48 (November 26 - December 2)	4,176	2,096	50.2%
Total	**16,516**	**9,204**	**55.7%**

Note: 'Number of cases' is the number of confirmed positive cases of COVID-19 in Ontario. Date was assigned to best align with sample collection date, which may differ from other PHO products. 'Number sequenced' is the number of cases sequenced for representative surveillance. Results may not be representative of Ontario overall, and do not include all samples tested for other reasons including travel, outbreak investigation, coroner's cases, reinfection or possible vaccine escape. 'Percentage sequenced' may be lower than the sampling proportion because not all cases are eligible to be sequenced (i.e. excludes samples with cycle threshold >30 or insufficient volume). For representative surveillance: details on the proportion of eligible samples sequenced by the OCGN can be found in the technical notes. Week was assigned based on earliest date available for a sample. Results for recent weeks are incomplete as not all sequencing and bioinformatics analyses were complete at the time of data extraction and will be included in subsequent reports.
Data sources: Public Health Case and Contact Management Solution (CCM), Ontario Health Data Platform - Public Health Analytic Environment (OHDP-PHAE)

On December 25, Ashleigh Hollowell from the Becker´s Hospital in U.S. published "COVID variant JN.1 dominates US" and highlights:
First detected in September, the latest COVID-19 variant to emerge, JN.1, has rapidly spread and now accounts for 44.1% of cases in the U.S., according toCDC data. A mutation L455S in the variant's spike protein could be to blame for its increased spread and some immune-evasive properties. However, the CDC hasnotedthat even so, "there is no evidence that JN.1 presents an increased risk to public health relative to other currently circulating variants."

Less than two weeks ago, around December 13, JN.1 accounted for only 21% of cases. Now that has more than doubled. Trailing JN.1, is another variant, HV.1, making up 22.1% of cases nationally. On December 26, Danna G. Smith from The New York Times, published "What to Know About the New Covid Variants"; HV.1 remains the leading variant in the U.S., but JN.1 now accounts for a growing share of cases.

Two variants, HV.1 and JN.1, now comprise roughlyhalfof all COVID-19 cases in the United States. HV.1 emerged in the United States at the end of the summer and has progressively made up a larger proportion of the circulating virus. According to the Centers for Disease Control and Prevention, it overtook a related variant, EG.5, in late October, and now accounts for just under 30 percent of COVID-19 cases.

EG.5. was the dominant variant in the United States for much of the late summer and early fall, but now accounts for just under nine percent of cases. Scientists have also been closely watching JN.1 and its parent variant, called BA.2.86.

The spread of JN.1 has rapidly increased, according to theWorld Health Organization. By late December, the variant accounted for over 20 percent of cases in the United States, while BA.2.86 accounted for just 1.6 percent.

Severe illness in older adults and people with underlying conditions is always a concern, as is long Covid in anyone who gets infected.

Experts say EG.5 and HV.1 do not pose a substantial threat, or at least no more of one than any of the other major variants that have circulated this year.

New data, published as a preprint paper in December, show that similarity extends to how well the updated vaccines perform against HV.1, suggesting the latest booster also offers some protection against it[32].

Given the variant's likeness, it's unclear exactly how HV.1 overtook EG.5, but one of the few additional mutations in HV.1 has likely given it an edge over its predecessor.

"Whenever a new variant dominates, then by definition it has an advantage," said Dr. Dan Barouch, the head of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center in Boston.

"And the advantage is either increased transmissibility or increased immune escape."

On December 27, GISAID published[33] "Receptor binding surveillance for complete genomes 2023-12-26", underlining:

New occurrence in the spike glycoprotein for the top 4 spreading lineages based on 31,981 sequences collected in the past 60 days.

HV.1

- H146K (895x): 410x in Canada, 115x in Sweden, 95x in USA/NY, 44x in USA/CA, 23x in New Zealand, 15x in Netherlands, 14x in USA/MN, 14x in France, 11x in USA/CO, 11x in Denmark.
- K444T (541x): 151x in Canada, 64x in USA/CO, 55x in USA/CA, 41x in USA/NY, 17x in Switzerland, 15x in USA/TX, 11x in USA/HI, 11x in USA/NJ, 10x in USA/IL.
- N149Q (47x): 20x in New Zealand, 11x in Canada.
- N148Q (46x): 20x in New Zealand, 11x in Canada.
- Y144L (38x): 20x in New Zealand, 11x in Canada.

JN.1

- T572I (152x): 55x in France, 27x in Denmark, 11x in Canada, 10x in USA/NJ, 10x in England.
- Q183H (123x): 30x in USA/NY, 28x in Scotland, 10x in Canada.
- L5F (58x): 13x in Denmark.
- E1150D (23x): 10x in France.

BA.2.86.1

- L455S (272x): 65x in France, 28x in Sweden, 25x in Spain, 23x in England, 16x in Netherlands, 14x in Italy, 14x in Denmark, 11x in Iceland.
- N487T (37x): 22x in Denmark.
- Y145P (37x): 18x in New Zealand, 11x in Canada.

The U.S. Centers for Disease Control and Prevention -CDC- in the COVID Data Tracker published the Weighted and Nowcast Estimates in United States for 2-Week Periods in 12/10/23-12/23/23[34], accessed on December 31, 2023, specifies the prevalent five SARS-CoV-2 variants in U.S. JN.1 is the most prevalent (44.2%), followed by HV.1 (22.6%), JD.1.1 (5.6%), HK.3 (5.5%) and EG.5 (5.5%).

The U.S. Region 7 -Iowa, Kansas, Missouri, and Nebraska- (28.4%) and the Region 3 -Delaware, D.C.- Maryland, Pennsylvania, Virginia, and West Virginia- (25.6%) shows the highest HV.1 prevalence around the country.

Data recorded by the authors shows the U.S. and Worldwide SARS-CoV-2 variant prevalence average in the weeks December 11-17 and December 18-24 shows (-- denotes no data from previous week)[35,36].

In the United States (Prevalence and Difference from the Previous Week):

Week December 11-17; HV.1 (27.62%, +0.14), JN.1 (8.93%, --), (FL.1.5.1 (4.35%, -0.60), JD.1.1 (4.05%, --) and HK.3 (3.87, --).

Week December 18-24; HV.1 (26.23%, -1.29), JN.1 (14.39%, +5.46), JD.1.1 (3.90%, -0.15), FL.1.5.1 (3.38%, -0.97), and HK.3 (3.45%, -0.42).

Worldwide as of December 24, 2023:

JN.1 (25.7%, --), HV.1 (13.2%, -3.3), JN.1.1 (7.0%, --), HK.3 (4.6%, -5.6) and EG.5.1.1 (1.3%, -2.8).

No data from CDC and SARS-CoV-2 Variant Dashboard on week December 25-31.

About JN.1, the prevalent SARS-CoV-2 variant at the end of 2023, U.S.-CDC published on 19 December 2023 "Initial Risk Evaluation of JN.1, 19 December 2023" and states[37]:

JN.1 is a descendent lineage of BA.2.86, with the earliest sample collected on 25 August 2023.

In comparison with the parent lineage BA.2.86, JN.1 has the additional L455S mutation in the spike protein.

As of 16 December 2023, there were 7,344 JN.1 sequences submitted to GISAID from 41 countries, representing 27.1% of the globally available sequences in epidemiological week 48 (27 November to 3 December 2023).

The countries reporting the largest proportion of JN.1 sequences are:

France (20.1%, 1552 sequences), the United States of America (14.2%, 1072 sequences), Singapore (12.4%, 934 sequences), Canada (6.8%, 512 sequences), the United Kingdom (5.6% 422 sequences), and Sweden (5.0%, 381 sequences).

Globally, there has been a rapid increase in the proportion of JN.1 reported, with its global prevalence at 27.1% in epidemiological week 48. This is a substantial rise from the data reported four weeks prior (week 44, 30 October to 5 November 2023), when the global prevalence of JN.1 was 3.3%.

This rapid growth is observed across all the three WHO regions with consistent sharing of SARS-CoV-2 sequences.

The region of the Americas (AMR), the Western Pacific (WPR) and the European (EUR) regions, with the largest increase seen in WPR from 1.1% in epidemiological week 44 to 65.6% in epidemiological week 48.

The JN.1's derived BA.2.86.1 replication kinetics on primary nasal epithelial cells (hNEC) have been observed to not be higher than other XBB-derived variants.

However, it remains to be determined whether the high transmissibility of JN.1 in humans is also associated with enhanced fitness in primary hNECs and other cell types, and how much of that is linked to non-spike mutations.

About the L452R and A475V S-protein mutations in HV.1, the literature reviewed shows:
The L452R spike protein mutation has appeared in several lineages[38].

In this mutation, there is a leucine to arginine substitution at amino acid 452.

The mutation is thought to increase immune evasion and ACE2 binding.

This mutation was observed in both the U.S. and Europe in 2020, before increasing in prevalence in January 2021.

It is notably present in the CAL.20C variant that has become widespread in California, particularly in Los Angeles.

It is also notably present in the B.1.617 variant.

Laboratory studies have found that specific monoclonal antibody treatments may not be as effective in treating COVID-19 caused by variants with the L452R or E484K mutations.

The name of the mutation, L452R, refers to an exchange whereby the leucine (L) is replaced by arginine (R) at position 452.

L452R is found in both the Delta and Kappa variants which first circulated in India, but have since spread around the world.

L452R is a relevant mutation in thisstrain that enhances ACE2 receptor binding ability and can reduce vaccine-stimulated antibodies from attaching to this altered spike protein.

L452R, some studies show, could even make the coronavirus resistant to T cells, that are necessary to target and destroy virus-infected cells.

They are differentfrom antibodies that are useful in blocking coronavirus particles and preventing it from proliferating.

A475V, in the spike protein substantially reduced the neutralizing activities of monoclonal antibodies and convalescent sera[39].

In addition, the A475V mutation alone moderately reduced the neutralizing activity but completely abolished the neutralizing effect of mAb 1D1 when F486V or L452R were also present.

In recent weeks, it has emerged that many of the Flip´s sub lineages have further gained the S:A475V mutation, previously seen in a few BA.2.75* descendants (BL.1.5 and BN.1.8)[40].

At the time of the writing, Flips + A475V lineages (such as JD.1.1, FL.15.1.1, GW.5.1.1, and GW.5.3.1, as well as many GK.*s) are among the few lineages resisting the fitness of JN.1 in predictive models.

Yunlong Cao´s lab recently communicated that S:A475V confers evasion to class 1 antibodies *in vitro*[41].

A475V has also appeared in the BA.2.86.1 descendant JN.4.

Since November 2023 Flips are suffering competition from the fast-growing JN.1* sublineages.

In conclusion, SARS-CoV-2 is again confirming its incredible plasticity in escaping the consolidating human immune response.

Since S:F456L, S:L455F, and S:A475V do not occur in the recently marketed XBB.1.5-based "updated" vaccines, the extent to which nAbs in vaccine recipients will provide protection from severe disease remains to be established.

Epidemiological monitoring is highly recommended to assess the relationships between specific sublineages and increased clinical severity.

Notably, some RBD variants such as A475V and F490L have been confirmed to have decreased

sensitivity to both human sera and multiple neutralizing mAbs[42].

A475V reduced the sensitivity to 6 mAb out of the 13 mAb used in this study, whereas F490L reduced the sensitivity to neutralization by 3 mAbs.

It is possible that antibodies in convalescent sera are able to neutralize these critical epitopes targeted by these mAbs that are known to disrupt the binding of the S protein to hACE2 receptor[43,44,45,46].

The A475V could weaken thehydrogen bondand hydrophobic interaction[46], whereas F490L may erode the hydrophobic interaction between molecules[43].

The World Health Organization, in the Executive Summary "Initial Risk Evaluation of JN.1", published on December 19, 2023, underlines[47]:

The World Health Organization on December 26, classified the JN.1 coronavirus strain as a "Variant of Interest", as a separate VOI from the parent lineage BA.2.86.

They said that current evidence shows risk to public health was low from the strain.

JN.1 is a descendent lineage of BA.2.86, with the earliest sample collected on 25 August 2023.

In comparison with the parent lineage BA.2.86, JN.1 has the additional L455S mutation in the spike protein. This rapid growth is observed across all the three WHO regions with consistent sharing of SARS-CoV-2 sequences (the region of the Americas, the Western Pacific and the European regions).

Based on its genetic features, JN.1 may possess some antigenic advantage evading previous immunity. With the limited data at this stage, the available evidence on JN.1 does not suggest additional public health risks relative to the other currently circulating Omicron descendent lineages.

While there is a rapid increase in JN.1 infections, and likely increase in cases, available limited evidence does not suggest that the associated disease severity is higher as compared to other circulating variants. The risk evaluation will be updated as more evidence arises

However, it remains to be determined whether the high transmissibility of JN.1 in humans is also associated with enhanced fitness in primary hNECs and other cell types, and how much of that is linked to non-spike mutations.

Conclusions

HV.1 exhibits:

- Similar transmission rate than EG.5.1*.
- A greater evasive capacity of immune-generated antibodies than EG.5.1*.
- To produce similar symptoms that of other Omicron variants.
- Are expected not to produce an increase in hospitalizations and mortality rate and,
- The SARS-CoV-2 vaccines recently developed by Pfizer and Moderna, must be effective against this Omicron subvariant.

The L452R mutation is thought to increase immune evasion and ACE2 binding.

This mutation was observed in both the U.S. and Europe in 2020, before increasing in prevalence in January 2021, as it is notably present in the CAL.20C variant that has become widespread in California, particularly in Los Angeles.

L452R is a relevant mutation in thisstrain that enhances ACE2 receptor binding ability and can reduce vaccine-stimulated antibodies from attaching to this altered spike protein.

L452R could even make the coronavirus resistant to T cells, that are necessary to target and destroy virus-infected cells.

The A475V mutation alone moderately reduced the neutralizing activity but completely abolished the neutralizing effect of mAb 1D1 when F486V or L452R were also present.

A475V substantially reduced the neutralizing activities of monoclonal antibodies and convalescent sera.

Some RBD variants such as A475V and F490L have been confirmed to have decreased sensitivity to both human sera and multiple neutralizing mAbs.

A475V reduced the sensitivity to 6 mAb out of the 13 mAb used in this study, whereas F490L reduced the sensitivity to neutralization by 3 mAbs.

For now, the SARS-CoV-2 variant HV.1 does not seem harmful in terms of creating a deadly disease but is still contagious enough to be ignored.

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