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REVIEW ARTICLE

Covid-19 variants: Impact on transmissibility and virulence

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Abstract

The genetic evolution of SARS-CoV-2 began in February 2020, with G614 spike protein strains superseding D614 strains globally. Since then with each subsequent mutations, the SARS-CoV-2 variants of concern, namely Alpha, Beta, Gamma, Delta and Omicron, superseded the previous one to become the dominant strain during the pandemic. By the end of November 2022, the Omicron variant and its descendent lineages account for 99.9% of sequences reported globally. All five VOCs have mutations located in the RBD of the spike protein, resulting in increased affinity of the spike protein to the ACE2 receptors resulting in enhanced viral attachment and its subsequent entry into the host cells. In vitro studies showed the mutations in spike protein help increase the viral fitness, enhancing both transmissibility and replication. In general, Alpha, Beta, Gamma, and Delta variants, were reported with higher transmissibility of 43–90%, around 50%, 170–240%, or 130–170% than their co-circulating VOCs, respectively. The Omicron however was found to be 2.38 times and 3.20 times more transmissible than Delta among the fully-vaccinated and booster-vaccinated households. Even the SARS-Cov-2 Omicron subvariants appear to be inherently more transmissible than the ones before. With the broader distribution, enhanced evasion, and improved transmissibility, SARS-CoV-2 variants infection cause severe diseases due to immune escape from host immunity and faster replication. Reports have shown that each subsequent VOC, except Omicron, cause increased disease severity compared with those infected with other circulating variants. The Omicron variant infection however, appears to be largely associated with a lower risk of hospitalisation, ICU admission, mechanical ventilation, and even a shorter length of hospital stay. It has been shown that the relatively much slower replication of the Omicron variants in the lung, resulted in a less severe disease.

Keywords: Covid-19 variants, subvariants, sublineages, characteristics, transmissibility, virulence

INTRODUCTION

Ever since COVID-19 was declared a global pandemic by the World Health Organisation (WHO) in March 2020, by 1 December 2022, 639,572,819 confirmed cases and 6.615,258 (1.04%) deaths have been reported globally.[1] In Malaysia, from 3 January 2020 to 1 December 2022, 4,992,168 confirmed cases of COVID-19 with 36,684 deaths were reported to WHO.[1]

Meanwhile, like the other RNA viruses, SARS-CoV-2, while adapting to their new human and even animal hosts, continue to evolve genetically with the development of mutant variants and subvariants that have different characteristics from its ancestral strains. The factors that drive the viral evolution include: selective pressures exerted by host responses, replication in other species and transmission back to humans; prolonged replication in immunocompromised hosts; RNA-dependent RNA polymerase (RdRp) mutations that interfere with the virus's proofreading function, or deletions that are not detected by its proofreading machinery.

The genetic evolution of SARS-CoV-2 began in February 2020, with G614 spike protein strains superseding D614 strains globally. The change at position 614 in the spike protein appeared to enhance viral replication, leading to higher transmissibility, but no evidence that it caused more severe disease or was better able to evade host immune responses.[2]

Each subsequent SARS-CoV-2 variants of

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concern strain superseded the previous one to become the regionally or globally dominant strain during the pandemic. All of them were reported to manifest diverse transmission dynamics, variable responses to vaccines and different impact on infection outcome.

Since November 2021, WHO reported that more than 200 countries around the world have reported SARS-Co-V-2 variants of concern and the Omicron variant has been detected by 76 countries. In fact, from 28 October to 28 November 2022, the Omicron variant and its descendent lineages account for 99.9% of sequences reported globally.[3]

Classification of COVID-19 variants

Monitoring and assessing of the COVID-19 variants actually began since January 2020 in collaboration with the currently named WHO Technical Advisory Group on Virus Evolution (TAG-VE), and the WHO COVID-19 reference laboratory network, with representatives from GISAID, Nextstrain, Pango as well experts in virological, microbial nomenclature and communication from several countries and agencies.

The letters of the Greek Alphabet continue to be used by WHO with the term 'index virus' for the genomic sequence of SARS-Cov-2 identified from the first cases in December 2019. Since the late 2020 onwards, as listed in Table 1[5], Variants of Concern (VOCs), Variants of Interest (VOIs) and Variants Under Monitoring (VUM) continue to be assigned based on their increased risk to global public health. A total of five VOCs, namely Alpha, Beta, Gamma, Delta and Omicron, have so far been assigned.[1] On 1 December 2022, the Omicron (B.1.1.529) variant remained as the only variant of concern globally, including Malaysia.[5] In Malaysia, all the previous VOCs, except the Gamma variant, were detected.[6] As for the eight previous circulating VOIs, the Eta, Theta and Kappa variants were sequenced in Malaysia.[7]

The Omicron subvariants began appearing towards the end of 2021, when several countries experienced a surge in cases driven by Omicron subvariant BA.1 and its descendent lineages. To date, there have been more than 58 BA.1 descendent sublineages assigned a PANGO designation. Following a wave of BA.1, several countries across several WHO regions experienced a wave of infection due to the Omicron BA.2 sublineage. BA.2 has over 218 descendent sublineages, including BJ.1, XBB, BA.2.75 and BA.2.3.20. As for BA.3 and its descendent lineage, they have been reported from 29 countries, with a global prevalence of 1% in week 41 (10 to 16 October), with no reports of BA.3-driven waves.

The emergence of BA.4 and BA.5 however, led to a significant rise in cases and deaths globally. BA.5 and its descendent lineages continue to be dominant globally, with dominance differing by country. Among BA.5 descendent lineages, BA.5.2, BA.5.2.1, BF.5 (BA.5.2.1.5) and BF.7 (BA.5.2.1.7) are the most prevalent sublineages.[3] Figure 1 shows the phylogenetic relationship of these Omicron subvariants.[4]

With the widespread transmission of the Omicron variants and their increased viral diversity across the globe, as listed in Table 2[3] and Table 3[5], WHO added the categories "Omicron Subvariants of Concern" and "Omicron subvariant under monitoring" to the variant tracking system.[5] So far, the Omicron subvariants detected in Malaysia are BA.1, BA.1.1, BA.2, BA.5 and XBB.[8-10]

Characteristics of COVID-19 variants

All five of the reported VOCs, Alpha (B.1.1.7); Beta (B.1.351); Gamma (P.1); Delta (B.1.617.2); and Omicron (B.1.1.529) have mutations in the receptor-binding domain (RBD) and the N-terminal domain (NTD) of the spike protein. The N501Y mutation that is located on the RBD, common to all variants except the Delta variant, results in increased affinity of the spike protein to angiotensin-converting enzyme 2 (ACE2) receptors thereby enhancing the viral attachment and its subsequent entry into the host cells. Along with NTD, RBD serves as the dominant neutralisation target and facilitates antibody production in response to antisera or vaccines.[11]

It was also reported that a single mutation of N501Y alone increases the affinity between RBD and ACE2 approximately ten times more than the ancestral strain (N501-RBD). It was also found that the binding affinity of the Beta (B.1.351) and Gamma (P.1) variants with mutations N417/K848/Y501-RBD and ACE2 was much lower than that of N501Y-RBD and ACE2.[12]

Alpha (B.1.1.7) variant

In late December 2020, the Alpha variant or GRY (formerly GR/501Y.V1), was reported in the UK based on whole-genome sequencing of samples from patients who tested positive for SARS-CoV-2.[13]

It contains 17 amino acid-altering mutations

Table 1: COVID-19 variants

WHO label (Pango lineage) GISAID clade [Nextstrain clade]	Earliest documented samples	Date of Designation
Variants of Concern (VOC)		
Omicron (B.1.1.529, including BA.1, BA.2, BA.1/BA.2 recombinant, BA.3, BA.4 and BA.5 and descendent lineages) GR/484A [21K, 21L, 21M, 22A, 22B, 22C, 22D]	Multiple countries, Nov-2021 # *Malaysia, 08-11-2021*	VUM: 24-Nov-2021 VOC: 26-Nov-2021
Previous Circulating Variants of Concern (VOC)		
Alpha (B.1.1.7) GRY [20I(V1)]	UK, Sept-2020 # *Malaysia, 28-12-2020*	VOC: 18-Dec-2020 Previous VOC: 09-Mac-2022
Beta (B.1.351) GH/501Y.V2 [20H (V2)]	S. Africa, May-2020 # *Malaysia, 01-12-2020*	VOC: 18-Dec-2020 Previous VOC: 09-Mac-2022
Gamma (B.1.1.28.1, P.1) GH/501Y.V3 [20H (V3)]	Brazil, Nov-2020	VOC: 11-Jan-2021 Previous VOC: 09-Mac-2022
Delta (B.1.617.2) G/478K.V1 [21A, 21I, 21J]	India, Oct-2020 # *Malaysia, 09-03-2021*	VOI: 4-Apr-2021 VOC: 11-May-2021 Previous VOC: 07-Jun-2022
NO current circulating VOI & Variants Under Monitoring (VUM) **Previous Circulating Variants of Interest (VOI)**		
Epsilon (B.1.427; B.1.429)	USA, Mar-2020	VOI: 5-Mac-2021 Previous VOI: 6-Jul-2021
Zeta (B.1.1.28.2, P2)	Brazil, Apr-2020	VOI: 5-Mac-2021 Previous VOI: 6-Jul-2021
Eta (B.1.525) #	Multiple Countries, Dec-2020	VOI:17-Mar-2021 Previous VOI: 20-Sep-2021
Theta (P3) #	Philippines, Jan-2021	VOI: 24-Mar-2021 Previous VOI: 6-Jul-2021
Iota (B.1.526)	USA, Nov-2020	VOI: 5-Mac-2021 Previous VOI: 20-Sep-2021
Kappa (B.1.617.1) #	India, Oct-2020	VOI: 4-Apr-2021 Previous VOI: 20-Sep-2021
Lambda (B.1.1.1.37, C.37)	Peru, Dec-2020	VOI: 14-Jun-2021 Previous VOI: 9-Mac-2022
Mu (B.1.621; B.1.621.1)	Colombia, Jan-2021	VOI: 30-Aug-2021 Previous VOI: 9-Mac-2022

COVID-19 Variants detected in Malaysia

in the viral genome. Of these, eight mutations (Δ69-70 deletion, Δ144 deletion, N501Y, A570D, P681H, T716I, S982A, D1118H) are in the spike (S) protein. N501Y shows an increased affinity of the spike protein to ACE 2 receptors, enhancing the viral attachment and subsequent entry into host cells.[14]

It has also been recently reported that Alpha mutations outside the S protein region led to a suppressed host innate immune response, indicating the possibility that the S protein region is not the only region important for immune defence.[15]

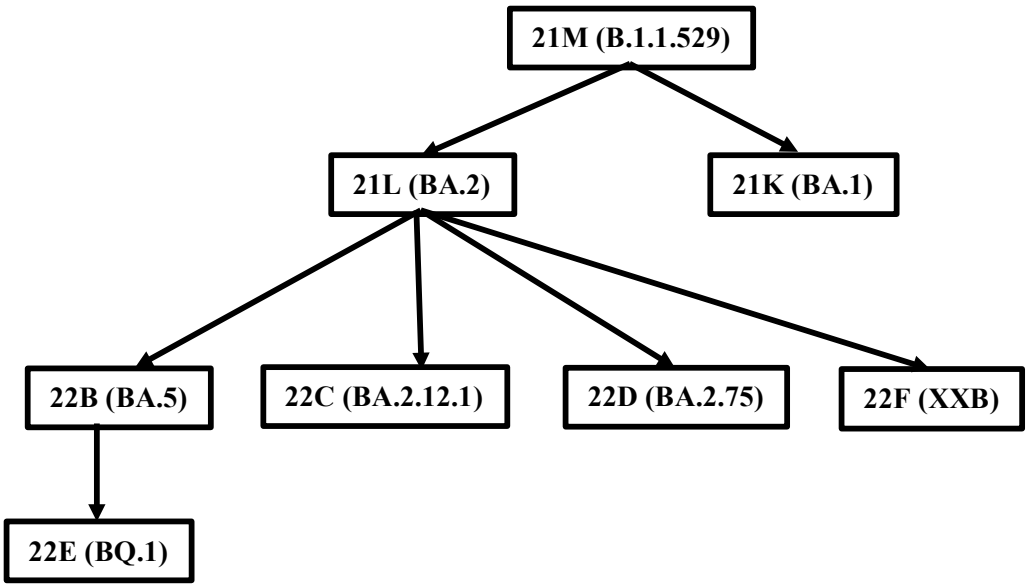

FIG. 1: Phylogenetic Relationship of Omicron clades (*Hodcroft EB*. 2021)[4]
Modified from http://covariants.org/

Table 2: COVID-19 Omicron Subvariants of Concern

Pango lineage	Earliest documented samples
BA.1 # (B.1.1.529.1)	UK, 02-09-2021
BA.2 # (B.1.1.529.2)	UK, 21-09-2021
BA.3 (B.1.1.529.3)	Poland, 23-11-2021
BA.4 (B.1.1.529.4)	UK, 07-01-2022
BA.5 # (B.1.1.529.5)	USA, 15-11-2021

COVID-19 Omicron VOC Subvariants detected in Malaysia.

Table 3: COVID-19 Omicron Subvariants Under Monitoring

Pango lineage (Nextstrain clade) [GISAID clade]	Relationship to circulating VOC lineages	Earliest documented samples
BA.5 # (22B, 22E) [GRA]	BA.5 sublineages (e.g. BF.7, BF.14, BQ.1, BQ.1.1)	07-02-2022
BA.2.75 (22D) [GRA]	BA.2 sublineage	31-12-2021
BA.4.6 (22A) [GRA]	BA.4 sublineage	20-07-2020
XBB # (-)	Recombinant of BA.2.10.1 and BA.2.75 sublineage, i.e. BJ1 and BM.1.1.1 with a breakpoint with S1	13-08-2022
BA.2.3.20 (21L) [GRA]	BA.2 sublineage	15-08-2022

COVID-19 Omicron Subvariants under monitoring detected in Malaysia.

Beta (B.1.351) variant

The Beta variant or GH501Y.V2 that resulted in the second wave of COVID-19 infections, was first detected in South Africa in October 2020 and rapidly became the dominant strain in the country.[16] It then went on to spread in multiple countries worldwide.

It contains nine mutations (L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, and A701V) in the spike protein, of which three mutations (K417N, E484K, and N501Y) are located in the receptor-binding domain (RBD). These appear to increase the binding affinity for the ACE receptors in the respiratory tract and confer some level of resistance to neutralising antibodies. A growth advantage in the respiratory tract contributes to its higher transmissibility.[17,18]

The E484K mutation has been shown to affect the binding of serum polyclonal neutralising antibodies, reducing antibody neutralisation, thus acquired protection from previous infections and vaccination can be evaded.[19] As for the K417N mutation in the S protein, it increases the ability of the S proteins to bind to ACE2 receptor, thereby increasing the transmissibility of the variant.[20] The L18F mutation in S protein however, was reported to compromise the interaction of neutralising antibodies and possibly hinder vaccine effectiveness and any relevant antibody-based therapies.[21]

Gamma (B.1.1.248/B1.1.28/P.1) variant

The third variant of concern, also known as GR/501Y.V3, was first detected in Brazil on 22 September 2020. Like the beta variant, this gamma variant also have reduced neutralisation by monoclonal antibody therapies, convalescent sera, and post-vaccination sera.[22]

This variant acquired 17 mutations, of which ten are located in the spike protein (L18F, T20N, P26S, D138Y, R190S, H655Y, T1027I V1176, K417T, E484K, and N501Y). Three mutations (N501Y, K417T, E484K) are located in the RBD, similar to the beta variant.[23]

The E484K and N501Y mutations resulted in an increase of receptor binding of Gamma S protein to ACE2 receptors, thus increasing the ability of the virus to infect host cells. However, K417N/T mutation showed a decreased binding affinity, which is the opposite of what was reported for the K417N mutation of the Beta variant.[24]

Delta (B.1.617.2) variant

This fourth variant of concern, a member of the sublineage group of a related B.1.617, was initially identified in December 2020 in India. Within one month the WHO classified it as a VOC in May 2021 when it became the dominant strain worldwide.

The B.1.617.2 variant harbours ten mutations (T19R, (G142D*), 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N) in the spike protein. Notable mutations such as L452R, T478K and P681R are associated with a possible increase in transmission rate and enhanced immune escape.[25,26] It has been found that the L452R + T478K double mutations increase the receptor-binding affinity of SARS-Cov-2, making it more stable, thereby increase transmissibility.[27] The Delta variant also has the ability to diversify into prominent sub-lineages, such as the AY sublineage.[28] In Malaysia, the AY.4.2 Delta subvariant was detected in late October 2021.[29]

Omicron variant

This Omicron variant was first identified in South Africa on 12 October 2021 and Botswana on 11 November 2021 after a surge in the number of cases of COVID-19.[30] By December 2021 it was responsible for 98.4% of new cases sequenced in South Africa.[31] Globally, since January 2022, Omicron has been the dominant VOC, after replacing Delta.

The variant showed the highest number of mutations with more than 30 changes to the spike protein.[30] The reported mutations include T91 in the envelope, P13L, E31del, R32del, S33del, R203K, G204R in the nucleocapsid protein, D3G, Q19E, A63T in the matrix, N211del/L212I, Y145del, Y144del, Y143del, G142D, T95I, V70del, H69del, A67V in the N-terminal domain of the spike, Y505H, N501Y, Q498R, G496S, Q493R, E484A, T478K, S477N, G446S, N440K, K417N, S375F, S373P, S371L, G339D in the receptor-binding domain of the spike, D796Y in the fusion peptide of the spike, L981F, N969K, Q954H in the heptad repeat 1 of the spike as well as multiple other mutations in the non-structural proteins and spike protein.[32]

Initial studies suggest that Omicron variant shows a 13-fold increase in viral infectivity, and is 2.8 times more infectious than the Delta variant.[33] The Spike mutation K417N (also seen in the Beta variant) along with E484A is predicted to have an overwhelmingly disruptive effect, making Omicron more likely to have vaccine breakthroughs

IMPACT OF COVID-19 VARIANTS ON TRANSMISSIBILITY

Generally, SARS-CoV-2 variants manifested an increase in transmissibility among the human population.[34-36] *In vitro* studies showed that single mutation N501Y, D614G, L452R, and P681R and set mutations from Alpha, Delta, and Omicron in spike protein help increase the viral fitness, enhancing both transmissibility and replication, proving that except for evasion from neutralisation, mutations of SARS-CoV-2 can increase viral transmission.[37-42]

By early 2021 in England, the Alpha variant became the dominant strain due to its increased transmission that ranged from 43-90%.[43] In South Africa, the Beta variant was found to be around 50% more transmissible than the previously circulating variants.[16] As for the Gamma variant, Brazil estimated it to be 1.7- to 2.4-fold (i.e. 170-240%) more transmissible.[23] The Delta variant was found to be just as transmissible as the Gamma variant showing 130-170% transmissibility.[44]

The Omicron variant however is estimated to be even more transmissible than the Delta variant, especially among the vaccinated population.[45,46] A study conducted in Denmark, found that Omicron was 2.38 times and 3.20 times more transmissible than Delta among the fully-vaccinated and booster-vaccinated households. Even among the unvaccinated, transmission was 1.10 times higher.[47] This suggests it may be largely driven by immune evasion of vaccine-elicited protection of Omicron, and the inherent increase in transmissibility of the Omicron variant. Household transmission studies further corroborate the transmission advantage of Omicron. It was found in the UK that household secondary attack rates for Omicron consistently show higher values compared to Delta, that is 13.6% vs 10.1%.[48]

It was also found that even the SARS-Cov-2 Omicron subvariants are inherently more transmissible than the ones before. This was reported in Denmark when BA.2 (39% secondary attack rate) is more transmissible than BA.1(29% secondary attack rate).[49]

Evidence have shown that SARS-CoV-2 can also infect animals due to the sequence similarity between human ACE2 and other mammalian ACE2,[50,51] suggesting the existence of a human-to-animal transmission pathway. Studies on mink farms have also indicated that SARS-CoV-2 can transmit between human and mink and back to human.[52,53] These results show the possibility of SARS-CoV-2 evolution occurring during intra-animal populational transmission, and such mutant strain may be transmitted back to humans through animal-to-human transmission. More work though, needs to be done to demonstrate enhanced SARS-CoV-2 variant transmission to the natural animal population.

IMPACT OF COVID-19 VARIANTS ON VIRULENCE

With the broader distribution, enhanced evasion, and improved transmissibility, SARS-CoV-2 variants infection cause more heterogeneous outcomes in patients mainly in two ways: the stronger but comprehensive ability to cause severe diseases due to immune escape from host immunity and faster replication, or the strain-specific mutational impact on viral protein leading to diversity in pathogenesis.

There have been reports of the alpha variant showing increased severity of disease compared to those infected with other circulating forms of virus variants.[54] A large matched cohort study performed in the UK reported that the mortality hazard ratio of patients infected with alpha variant was 1.64 patients with previously circulating strains.[55] There are also additional reports of increased risk of hospitalization and severe cases of death related to Alpha, Beta, or Delta variant infections.[56,57]

A report in UK found that the hospitalisation rates due to Delta variant were relatively higher compared with non-Delta cases.[58] However, another report in UK[59] looked at the risk of hospitalisation and severe disease with Omicron compared to Delta and calculated a 41% reduced risk of a hospitalisation resulting in a stay of one or more nights.

The Omicron variant thus, showed a comparative decrease in disease severity. Using a record linkage approach[60], a study in South Africa found that laboratory-confirmed SARS-CoV-2 infected individuals with SGTF, as a proxy for Omicron, had lower odds of severe disease. In Canada, preliminary data from cohorts of patients with onset date between 22 November and 25 December 2021 also show a reduced risk of hospitalization and death for Omicron compared to Delta after adjusting for vaccination status, further suggesting a reduction in intrinsic severity.[61] Therefore, Omicron variant infection appears to be largely associated with a lower risk of hospitalisation, ICU admission, mechanical ventilation, and a shorter length of hospital stay

than the Delta variant infection.[56,62]

It is known that virulence is associated with higher viral titres in the upper respiratory tract, leading to higher viral loads in the lower respiratory tract and trigger more severe disease. Using samples from the lower respiratory tract, it was found that the Omicron variant replicates up to 70 times faster in the human bronchi compared to the Delta variant and the wild-type SARS-CoV-2 virus. In contrast, the Omicron variant showed relatively much slower replication in the lung, resulting in a less severe disease.[63] A similar finding was reported in the United Kingdom where Omicron showed a reduction in replication kinetics compared to Delta and the original SARS-CoV-2 strain.[64] These observations support the notion of a reduction in intrinsic severe clinical presentation of patients infected with the Omicron variant.

CONCLUSION

The unprecedented speed of the COVID-19 vaccine development and intensive global mass vaccination efforts including vaccine boosters prevented at least 14 million deaths from COVID-19 in 185 countries and territories within one year.[65] The emergence of these SARS-CoV-2 variants and subvariants has and continue to challenge the significant progress made in limiting the spread of this devastating infection.

Even though most of the current vaccines used the SARS-CoV-2 spike protein as the main antigenic target based on the original Wuhan virus, the vaccines remain effective against the COVID-19 variants but with decreasing effectiveness. A recent systemic review and meta-analysis found that the full vaccination series of COVID-19 vaccines is highly effective against Alpha (88% VE) variant, and moderate against Beta (73% VE), Gamma (63% VE), and Delta (78% VE) variants. The Omicron variant however showed only 55.9% vaccine effectiveness.[66]

Even so, it is important to note that VE estimates against the Omicron variant remain high for severe disease. The first booster vaccination substantially improves VE up to 80.8% for all outcomes.[66] It was reported however, that the VE declines more in the first six months after the first booster vaccination for symptomatic disease and infection than it does for severe disease.[67] It was also reported in five studies that the VE for the Omicron variant for second booster dose vaccination, declines over time as has been seen with the first booster dose.[68-71] Fortunately, with the authorised availability of the bivalent vaccine that contains the original SARS-CoV-2 plus the Omicron BA.4/5 strains, a recent evaluation found the second booster, using the bivalent BA4.5 vaccine, to be more immunogenic than the original monovalent vaccine against the circulating Omicron sublineages, including the globally prevalent BQ.1.1.[72]

What needs to continue is to develop new vaccine combinations in time to address the new COVID-19 variants in order to reduce its spread, thereby reducing the numbers inflicted with severe disease and ultimately the number of deaths.

Conflict of interest: The author declares no conflicts of interest.

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