Interpreting the Omicron drama

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Omicron variant of SARS-CoV-2 emerged in southern Africa in November 2021, showing more mutations on the spike protein gene than other variants, high efficiency in transmission, immune evasion, causing a mild disease, mostly upper respiratory and low mortality. Its proximate parent is unknown. We argue that its evolutionary pathway was reverse zoonosis in rodents, acquiring rodent adaptation mutations and subsequently infecting humans as zoonosis – conceptually a 'deviant' with antigenic shift rather than variant with antigenic drift; its pathogenesis is modified by its cell entry pathway resulting in the absence of syncytia, low virus load, sparing lungs of pneumonia and hypoxia.

Keywords: Omicron variant of concern, reverse zoonosis, SARS-CoV-2.

THE dramatic entry of the Omicron variant of SARS Coronavirus type 2 (SARS-CoV-2) at the end of the second year of the COVID-19 pandemic took everyone by surprise. It was an unanticipated and unwelcome event in the storyline of the unfolding pandemic drama – posing a challenge to both scientific and public health experts.

This variant was detected first in South Africa and Botswana, spread very rapidly in the densely populated Gauteng province of South Africa, classified as B.1.1.529 and reported to the World Health Organization (WHO) on 24 November 2021 (ref. 1). It was frequently 're-infecting' those who were previously infected with earlier variants including Delta and causing 'break-through infections' in those vaccinated with two doses of Pfizer-BNTech mRNA vaccine. The twin properties of greater transmission efficiency and more efficient immune evasion than even the Delta variant led WHO to declare Omicron to be a Variant of Concern (VOC) on 26 November 2021 (ref. 1).

We attempt to interpret the causes and consequences of the emergence of Omicron by asking the following questions:

(1) What was the evolutionary pathway of Omicron?
(2) Why are its transmission efficiency higher, clinical syndrome milder, and case fatality rate (CFR) lower compared to other VOCs?
(3) What explains the high frequency of re-infections and breakthrough infections?

With answers to these questions, we speculate on the future trajectory of the pandemic and how it might impact our responses to the continued prevalence of COVID-19.

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The mystery behind the origin of Omicron variant

SARS-CoV-2 viral genome is single-stranded positive-sense RNA, similar to that of poliovirus[2]. Such viruses mutate slowly and predictably according to the molecular clock theory proposed for polioviruses[3]. In the attenuated vaccine polioviruses, mutations on the gene (~1000 nuceotides) coding for the structural protein VP1, occur at a frequency of approximately 1% per year if they remain in transmission among children. When there are 0.6% (for type 2 poliovirus) and 1% (for types 1 and 3) mutations, the virus variant is designated vaccine-derived poliovirus (VDPV). When VDPV continues to circulate and causes polio in more than one child, signalling re-gained neurovirulence and transmission efficiency similar to wild poliovirus, the variant is called 'circulating VDPV'[3].

In the case of SARS-CoV-2, mutations on the spike protein gene are key for the emergence of variants. Spike protein gene consists of S1 (463 nucleotides), receptor-binding domain (RBD, 222 nucleotides) and S2 regions. When a variant has observable phenotypic change(s) that result in increased virulence, transmission efficiency or immune evasion, it is designated as VOC by the WHO.

Wuhan original SARS-CoV-2 with one mutation (D614G) caused the pandemic initially – therefore, we may call it the Founder Variant. The VOCs are Alpha, Beta, Gamma, Delta and Omicron; other variants, namely Epsilon, Zeta, Eta, Theta, Iota, Kappa and Mu are not of concern in terms of pandemic potential[4].

The whole genome sequence indicated that, unlike all earlier variants for which the Founder Variant was the proximate parent, Omicron's proximate parent was neither the Founder Variant nor Alpha, Beta, Gamma or Delta. All of the latter varied from the Founder Variant with only a small number of mutations on the spike protein gene, and each emerged in a specific geographic locality in 2020, chronologically, Alpha in the UK, Beta in South Africa, Gamma in Brazil and Delta in India. Alpha, Beta, Gamma and Delta

variants differed from their proximate parent Wuhan-D614G with 1, 3, 3 and 2 mutations on RBD and 5, 5, 7 and 7 mutations on S-1 respectively. In contrast, the Omicron has ~15 mutations on RBD and ~17 on S-1 (ref. 5).

Omicron was also unusual: it consisted of a few closely related sub-variants named BA.1, BA.2, BA.3, BA.1.1, BA.4 and BA.5 (ref. 6). In terms of transmission efficiency, BA.2 was the most transmissible, followed by BA.1. The BA.2 sub-variant of Omicron, which had greater transmissibility and possibly also greater immune escape properties, quickly replaced BA.1 in many countries, including India, Denmark, the Philippines, Qatar and Nepal and became either the dominant or the exclusive agent that caused the last wave of the pandemic everywhere. Further, re-infections with BA.2 variant have been reported shortly after BA.1 infection[7].

The primer in the commercially available PCR test kit does not amplify the *S* gene of BA.1 due to mutational changes; therefore, '*S*-gene target failure' is a marker to identify BA.1 sub-lineage of Omicron on a PCR test. This phenomenon does not occur with BA.2 sub-lineage.

Omicron spreads faster than Delta, and in some countries, the Omicron and Delta co-circulated, some individuals got double infections, and this resulted in the emergence of recognizable recombinants[8]. Such recombinants, for want of a globally agreed nomenclature, were named as X series, such as XA, XB, XC, XD and XE (ref. 6). As of this writing, XA to XS have been reported formally or informally. BA.1 and Delta recombinant were named XD and BA.1 and BA.2 recombinant were named XE (ref. 6).

As so many mutations cannot accumulate within less than two years of human community transmission, the emergence of Omicron remains a mystery. Therefore, alternate hypotheses are germane for exploring the origin of Omicron, as we consider here.

Possible origin of Omicron

Two hypotheses explain the acquisition of these many mutations in the second year of the pandemic. One, mutations accumulating in an immune-compromised individual with prolonged SARS-CoV-2 infection, and second, infection by reverse zoonosis in an animal species, enzootic transmission in that species with adaptive mutations, and eventual transmission as zoonosis, back to human subjects. Though there is evidence of plausibility in favour of both hypotheses, the second hypothesis seems more likely.

In a report from the UK, in three HIV-positive persons with prolonged SARS-CoV-2 (Alpha variant) infection, mutations associated with increased transmissibility and partial immune evasiveness were documented[9]. However, during the persistence of infection for 7–9 months, only 2–3 new mutations were detected in the RBD region. Therefore, the accumulation of ~15 mutations in RBD in less than two years is unlikely to have occurred in a single immune-compromised human host with chronic SARS-CoV-2 infection. Moreover, this pathway cannot explain the simultaneous appearance of several sub-variants.

The second hypothesis is supported by several pieces of evidence. That rodents were the animal hosts was proposed, investigated, and reported with evidence by Wei and colleagues from China[10].

Could SARS-CoV-2 acquire mutations faster in another animal than the slow pace observed in humans? Recently, in the US, a pet cat was found to have contracted infection by the Delta variant (AY.3) from its owner[11]. Large quantities of virus were shed in faeces, and the cat-adapted virus had several unique mutations that differed widely from Delta[11]. Thus, the molecular clock theory appears to break down during inter-species transmission and adaptation in a new host species.

Reverse zoonosis and enzootic transmission have been investigated in white-tailed deer in North America[12]. The enzootic virus was highly divergent, with 9 mutations on the spike protein gene. The most likely progenitor, the human virus variant was Beta VOC[12].

As the Beta VOC had earlier emerged in Southern Africa, is it possible that rodents in that region were infected by it? Investigators in Finland tested the susceptibility of the house mouse (*Mus musculus*) to SARS-CoV-2 by the nasal route[13]. Mice were susceptible to infection with Beta VOC but not with D614G or Alpha, Gamma or Delta VOCs[13]. Mice are not only readily infected by intranasal inoculation (for reverse zoonosis to occur in nature), but they also efficiently transmit the virus horizontally to cage mates, indicating the potential for enzootic spread in rodents[14].

Is there evidence that rodents could infect humans with SARS-CoV-2? Rodents in the Muridae family include two sub-families Murinae (mice and rats) and Cricetinae (golden or Syrian hamsters). While mice are naturally susceptible to Beta VOC, hamsters are naturally susceptible to Delta VOC[15]. In a pet store and its warehouse in Hong Kong, when the pet-shop owner got infected with SARS-CoV-2, all hamsters (imported from The Netherlands) were screened, and several were found to be infected with Delta VOC. On further investigation, other visitors to the pet shop were also found to have Delta VOC infection[15]. Therefore it is inferred that reverse zoonosis with SARS-CoV-2 infection had occurred in this hamster colony in the Netherlands, followed by hamster-to-hamster spread and subsequently zoonotic spread from them to human subjects[15].

Although this circumstantial evidence supports the theory of rodent adaptation, how rodents could get infected in the first place remains unanswered. Could rodent–human contacts in low-income households in Africa facilitate virus transmission?

In mid and low-income countries, in towns and villages, rats and house mice live in close proximity to human habitations. Rat bite is known to transmit bacterial and virus infections to humans. In lepromatous leprosy, with total loss of touch and pain sensations, fingers and toes are vulnerable to rodent bites while sleeping, explaining recurrent ulcers

and loss of tissue. Hantavirus pulmonary syndrome, Lassa fever and South American haemorrhagic fevers caused by Arenaviruses are transmitted from rats or mice through urine contaminating food grains or the floor in residences. House mice are nocturnal animals, and they do run around on floors; in many households, people sleep on mats on the floor. Thus even air-borne transmission in either direction – man-to-mouse and mouse-to-man is possible in environs with high rodent density. We have alerted colleagues in South Africa and WHO to explore if house and field rodents (mice and rats) have any evidence of infection with SARS-CoV-2.

This genetic and ecological circumstantial evidence prompt us to propose reverse zoonosis, circulation in rodent population and subsequent spread as a zoonosis in human subjects as the most probable theory of the evolution and emergence of Omicron VOC. We interpret the multiple sub-variants, their co-circulation and re-combinations as signals of the cross-species circulation with the resultant gene diversity followed by human re-adaptation of the Omicron variant. We are not aware of other hypotheses proposed and argued with evidence.

Why is clinical manifestation of Omicron milder than that of other VOCs?

To explore this question, it is important to ask how Omicron differs from the earlier variants in terms of virus–host cell interactions. For host–parasite interactions of pathogenic viruses, the surface motifs of the virus that bind to host cell receptors leading to the entry of viral genome are crucial. In order to infect cells, viruses interact with specific cell surface receptors. SARS-CoV-2, through its spike protein, binds with the ACE2 receptor located on the human host cell-surface. The spike protein is made up of three components S1, RBD and S2. RBD is nested within S1 subunit and harbours the receptor binding motif (RBM), and S2 can induce the fusion of the viral coat with the host cell membrane.

The process of cell entry of the virus requires proteolytic cleavage of the spike protein after attachment. This cleavage, in Beta coronaviruses, can be induced by either a serine protease on the host cell surface membrane called Trans-Membrane Protein Serine Protease 2 (TMPRSS 2) or by Cathepsin B or L located within the intra-cytoplasmic subcellular organelle, endosome.

If fusion is mediated by TMPRSS 2, the viral envelope fuses with the host cell membrane, and the viral genome automatically gains entry into the cytoplasm, where it replicates unrestricted by interferon. Now the entire cell membrane mimics the virus envelope, and adjacent cells fuse with the infected cell to form a syncytium, a mass of cytoplasm with many nuclei (a multi-nucleated giant cell), which acts as a highly productive factory of virus particles.

For the Cathepsin-mediated cell entry process, after binding, the virus-ACE2-receptor complex is internalized by endocytosis – and the membrane covering the endocytotic vesicle then fuses with the endosomal membrane and the viral RNA gains entry into the endosome. As the viral genome enters the endosome, viral replication is subject to restriction by Interferon-induced Trans Membrane Restriction Peptides (IFITM), which reduce viral replication and lead to the production of many truncated defective and non-infective viral particles. Infected host cells do not fuse with adjacent cells to form syncytia.

Earlier variants of SARS-CoV-2 used the TMPRSS 2 pathway predominantly, even though they could also use the Cathepsin pathway[15]. Omicron preferentially uses the Cathepsin-mediated pathway, resulting in less efficient viral replication than other variants[16].

Interestingly, expression of TMPRSS 2 is upregulated by androgens – this may partly explain the greater severity of COVID-19 in men than in women. As the Cathepsin-mediated pathway is androgen-independent, Omicron-induced disease in men may be no different than in women; we await clinical studies to check this out.

The differences between Omicron and other VOCs in virus–cell interactions have major implications for the pathogenesis of COVID-19. Reduced viral replication and lack of formation of syncytia are associated with an overall milder disease process. In the pulmonary alveolar cells (pneumatocysts) ACE2 receptor and TMPRSS 2 enzyme are universally co-expressed on the cell surface; therefore, earlier VOCs preferentially targeted the alveoli – the site of oxygen/carbon dioxide exchange between inspired air and capillary blood. In the lining cells of the upper airways, co-expression of the ACE2 receptor and TMPRSS 2 is patchy, but Cathepsin's expression in the endosomes is universal. Due to this differential expression of receptors and enzymes in the lining cells of the upper airways compared to the alveoli, Omicron VOC can readily infect the cells of the upper airways, larynx and bronchus while sparing the alveolar cells. This feature has been confirmed in primary nasal epithelial cell cultures[16].

Earlier VOCs caused a multi-system disease with lungs as the primary and predominant target organ – with bilateral viral pneumonia and inadequate oxygenation of blood resulting in hypoxia; gastrointestinal involvement was common, but cardiac, renal and neurological involvement was less frequent. A larger proportion of those infected needed hospital admissions, and mortality was high in the elderly and vulnerable, particularly men.

On the other hand, Omicron-induced disease is milder, with predominantly upper respiratory symptoms (sore throat and nasal congestion) and far less severe lung disease overall; multi-system involvement is mostly absent. In short, Omicron-induced illness resembles the 'common cold', and most patients recover over 3–7 days. There is abundant viral shedding from the upper airways and even in saliva – leading to air-borne transmission. Intra-family spread of infection, very common with the Delta variant, is nearly 100% with Omicron, making the family the unit of infection rather than the individual.

In early reports from China, the severe disease occurred in about 15% of those infected, and 8% needed ventilator support[17]. In India, data from Maharashtra showed a CFR of 2.75% during the first wave in 2020; 1.81% during the Delta-driven second wave and only 0.1% during the Omicron-driven third wave in January 2022 (ref. 18).

Studies from Canada, England, South Africa and Scotland also confirm that, compared to infection with the Delta variant, the risk of hospitalization and deaths due to infection with Omicron is much reduced[19]. While immunity acquired from previous infections or vaccination is probably an additional significant contributing factor to the reduced CFR of Omicron infection, its contribution to a reduction in CFR remains unquantified[20].

Indeed, if the disease caused by Omicron is so different, and as it emerged in 2021, should we not call it by a different name – such as COVID-21?

Why is transmission of Omicron more efficient?

Omicron VOC is far more transmissible than Delta, the most infectious SARS-CoV-2 variant during 2021.

Using Omicron and Delta isolates and an *ex-vivo* model of human alveolar and bronchial epithelial tissue, researchers from Hong Kong found that Omicron, compared to Delta, has 70-fold greater potential to infect bronchial mucosal cells than alveolar cells[21]. This is probably responsible for its higher transmission efficiency. The abundance of the virus in salivary samples (detected by RT PCR) accounts for the ease with which an infected person broadcasts the virus when he/she holds a normal conversation.

If the R_0 of D614G was 1.5–2, and that of Delta was calculated to be 3–5, the R_0 of Omicron seems even higher, at 10–12. While the other VOCs were spreading rapidly in immune-naive populations, when Omicron entered the picture, a large proportion of the population had already become partially immune to SARS-CoV-2 and its variants – and/or partially or fully vaccinated. Yet, Omicron was able to spread in all countries as if it were a new pandemic, and for this reason, the disease caused by Omicron may be more appropriately called COVID-21.

Why does Omicron evade immunity more efficiently?

Until now, the Spike protein of the (D-614G variant) and its gene sequences have been used exclusively to design diagnostic reagents for RT PCR and rapid antigen tests, and to develop most of vaccines against SARS-CoV-2. Omicron, with its many mutations, has such marked differences in its spike protein that the current serological tests are less suitable for assessing immunity; further, Omicron is better able to evade immunity from prior infection or prior vaccination as illustrated by the following *in vitro* and *in vivo* data.

In vitro, cell-culture studies using pseudo-typed SARS-CoV-2 variants demonstrated the dramatic escape of Omicron from neutralizing antibodies against the D614G variant[22].

Convalescent sera from subjects who had recently recovered from SARS-CoV-2 infection (by Alpha, Beta or Delta), as well as sera from subjects vaccinated with mRNA vaccines have been used to compare cross-neutralization by different variants of concern[23]. Cross-neutralization with convalescent sera, compared to the D614G reference strain, was reduced by only 1.2-4.5 fold for previous Variants of Concern, whereas against Omicron, it was reduced by 8.4 fold[24].

In vivo, previous monoclonal antibody cocktails (developed against S protein of D614G), such as LY-CoV016/LY-CoV555, REGN10933/REGN10987, AZD1061/AZD-8895, and BRII-196, used early in elderly and vulnerable to mitigate the severity of COVID, are relatively ineffective against Omicron-induced disease. Even Sotrivimab, a pan-Sarbecovirus monoclonal antibody, considered initially to show promise for treating early Omicron infection in the elderly and vulnerable, was found to be ineffective against Omicron BA.2 subvariant and authorization for its use was withdrawn by the US Food and Drug Administration in April 2022 (ref. 25).

Globally, all COVID-19 vaccines have performed much better against symptomatic infection due to all previous VOCs than against Omicron. In South Africa, when Omicron became the dominant circulating variant in hospitalized patients with COVID-19, vaccine effectiveness (VE) in subjects vaccinated with two doses was 93% for Delta but only 70% for Omicron[26].

Fortunately, during the same period, in subjects who had received a third (booster) dose of mRNA vaccine, the overall risk of hospitalization for COVID-19 declined by 68% compared to unvaccinated subjects. The net result was that fewer patients needed admission overall[26].

A test-negative case-control trial in the UK demonstrated the waning of VE against symptomatic Omicron infection – to 60% 2–4 weeks after a booster dose of mRNA vaccines; and further to 35% (with Pfizer) and 45% (with Moderna) at 10 weeks post-booster. However, VE in terms of preventing hospitalization was better (88%) in those who received a booster dose compared to those who had received only two doses of vaccines[27].

Omicron VOC, with its very different biologic behaviour, will have a major impact on the course of the pandemic and our response to it. This variant behaves like a new virus subtype, and the infections and diseases caused are so different that they may deserve to be called COVID-21 to distinguish it from COVID-19.

Is Omicron a mere variant or a 'deviant'?

The rapid acquisition of a large number of mutations in the RBD and the rest of the S protein domains in Omicron

indicates an 'antigenic shift' rather than 'antigenic drift', raising an important question: should it be called just another variant, or should it be called a subtype of SARS-CoV-2? Until the International Committee settles this question on Virus Nomenclature, we may call it a 'deviant', to highlight its differences and to distinguish it from other variants. However, the terms antigenic drift and shift have hitherto been used exclusively for influenza viruses but we are forced to borrow them to depict a wide variation in antigenic repertoire in real-world epidemiology.

The world faced the Omicron wave as if it were a new pandemic that started in 2021 rather than the third wave (for India), fourth wave (for South Africa and Zimbabwe) or fifth wave (for many European countries). Indeed, India had remained in the post-Delta endemic phase for 25 consecutive weeks before the Omicron wave (or pandemic) struck India. Once again, India has transitioned into a new endemic phase as of 17 February 2022 (ref. 28). We believe that, over time, this pattern will manifest in all other countries, and the pandemic will transition into a pan-endemic phase. That we hope will herald the end of the pandemic with no more waves. Without Omicron deviant, the world would already have been in the post-Delta endemic phase.

As we said earlier, the emergence of Omicron was a most unexpected turn of events. Though initially most unwelcome, with hindsight, perhaps the arrival of Omicron was a blessing in disguise. Countries such as those in Africa, with only 15–16% vaccination coverage, that are going through the Omicron wave may pay a far lower price than what would have been if Delta had preceded the Omicron wave.

Future trajectory and implications for endemic phase

Due to its universally high prevalence, Omicron has resulted in establishing very high population immunity (otherwise called 'herd immunity'). As a direct consequence, it appears to have brought the pandemic to an end in India, in the fourth week of February 2022 (ref. 29). We hope and expect this happy ending to be true for all other countries as well.

From the preceding discussion, it is evident that the emergence of the Omicron variant was an unusual development, not fitting in the evolutionary pathway of the previous VOCs, which originated from the parent Wuhan-D614G. The possibility of another rare occurrence due to a potential reverse zoonosis of SARS-CoV-2 is extremely unlikely. Therefore, we presume that it is most unlikely that we will witness another major wave caused by a newer SARS-CoV-2 variant after Omicron. However, Omicron is a family of sub-variants, and some have greater transmission efficiency than others. Whether one or more of them will predominate is unpredictable as of now. Subvariants BA.2, BA.4 and BA.5 or some recombinants may dominate the future – hence close watch on the prevalence of subvariants and recombinants is extremely important. (Note: Recently rats in several locations in New York have been found with Omicron infections, confirming its tendency to transmit as reverse zoonosis in Nature[30]. Currently Omicron subvariant XBB.1.16 is the predominant one in circulation in India. It is a recombinant of two Omicron variants, namely, BA.2.10.1 and BA.2.75.)

After the pandemic recedes in all countries, which we expect to occur in the coming weeks/months, there is likely to be a global pan-endemic state, with low numbers of cases and larger numbers of silent infections, the endemic transmission driven by new additions to the population on account of births and growth. Will Omicron be the sole surviving VOC globally, or will another VOC (such as Delta) co-circulate? Although impossible to predict without more information, we expect Omicron as the sole survivor of the endemic SARS-CoV-2 infection and consequent disease.

As the Omicron drama was unfolding, many vertebrate genera and species were found to be infected by SARS-CoV-2 from humans and not from the original source from which humans got infected. SARS-CoV-2 infection is currently enzootic in two free-ranging animal species, the white-tailed deer and the mule deer[12,31].

We have already speculated that rodents are enzootically infected in some parts of Africa. Once adapted to a wildlife species the virus, can continue to mutate, cross-infect other vertebrates and even spill over to humans[32]. Here, we have proposed that Omicron had taken such a route through rodents, but without direct evidence. It remains to be seen if any such cross-species evolutionary pathway will introduce new vagrants, and even if they do, will they spread among humans with extremely high herd immunity already achieved?

Therefore, it is in our best interests to keep up and enhance herd immunity through continued vaccination across a broad age range, for which national and global level vaccination policies must be formulated. However, during endemic transmission, especially with the relatively low virulence, the risk of severe disease, need for hospitalization and ICU care, and of death are likely to be very infrequent, and vaccines with serious adverse events after immunization (AEFI) may not survive the future benefit-risk analysis. In other words, only completely safe vaccines (without any life-threatening AEFI) may persist.

A final question is regarding the possibility of eradicating SARS-CoV-2 from human communities. As long as the infection was exclusively anthroponotic, without spill-over to animals, especially to animals susceptible to continued enzootic spread and the potential of zoonotic transmission to humans, the potential for eradication was good. However, with the emergence of Omicron illustrating that SARS-CoV-2 is no longer exclusively human, the probability of eradication is rated very low.

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