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Viral Load and Asymptomatic Virus Status of the SARS-CoV-2 Variants towards Influencing the Transmission

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

The Covid-19 virus (CoV) has worsened due to its transmissibility worldwide. Several millions of people have been infected since 2019 when it was first detected. Unpredictable impact and disruption created by the pandemic influence global financial or economic crisis. This motivated governments to encourage more vaccination to manage the spread and counter the pandemic, thereby breaking the chain. However, despite the level of vaccination against CoV, that has not been found to prevent an individual from being infected.

In addition, many transmission of SARS-CoV-2 occurs at the pre-symptomatic infection stage, which thus makes it difficult to contain. The impact of the vaccination and booster immunizations on viral load and transmissibility. There is a positive relationship where vaccination influences the transmission rate.

This study aims to identify how critical the viral loads and asymptomatic virus status of the SARS-CoV-s influence the transmission of Omicron and how the quantitative SARS-CoV-s viral load assay corresponds to the clinical outcome while managing Covid-19 infected patients.

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1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have resulted in an unprecedented global health pandemic of the 21st century. The Covid-19 virus (CoV) has thus created a worsened situation due to its transmissibility worldwide. As a result, several millions of people have been infected since 2019, when it was first detected.

The evolution of the virus has since occurred from the first time it was first discovered in the Wuhan region of China. Various variants have thus emerged regarding the characteristics and catastrophic impact they exhibit on infected individuals. SARS-CoV-2 is now diagnosed using the real-time reverse transcriptase polymerase chain reaction technique and reported using the binary assessments model for the test to indicate whether it is positive or negative. Another approach in the diagnosis involves the application of deep learning models to the various forms of medical imaging. Imaging such as the X-rays and computed tomography (CT) images in conjunction with the DL methods will help in the classification of Covid-19 versus pneumonia [1,2]. In terms of sensitivity, CT scans & chest X-rays have been reported to have high sensitivity values of 98 and 69%, respectively [3].

Unpredictable impact and disruption created by the pandemic influence global financial or economic crisis. This motivated governments to encourage more vaccination to manage the spread and counter the pandemic, thereby breaking the chain [4]. However, despite the level of vaccination against CoV, that has not been found to prevent an individual from being infected.

Many transmission of SARS-CoV-2 occurs at the pre-symptomatic infection stage, which thus makes it difficult to contain [5,6]. In addition, unlike influenza, most SARS-CoV-2 usually do not transmit the virus, while just a small percentage of those transmit and infect a large population [5].

Several bodies of data have been provided to study the characteristics of those emerging CoV variants that have remained a major threat or concern to different regions worldwide. For instance, those emerging ‘variants of concern’ (VOC) possess unique viral characteristics that are being studied.

The goal is to understand the relationship with viral transmissibility, immune evasion, viral load, disease severity, and lethality among the patients that are already infected—getting to understand the available scientific evidence from both the clinical studies and animal models needed to be reviewed to understand the relationship between the viral load and covid-19 prognosis with vaccine efficacy [4].

In addition, the viral load dynamics and kinetics among both the vaccinated and unvaccinated populations have been further studied using longitudinal follow-up data. However, because of the scarcity of such studies, many researchers have found this approach limited.

2. METHODS

A literature search was undertaken using PubMed/Medline, Viruses, Frontiers, and PLOS ONE journal databases. A combination of search tags or keywords were used, including the SARS-CoVs viral load, Omicron viral load, COVID-19 viral load, quantitative viral loads, viral dynamics, Viral kinetics, associated with severity, transmissibility, household contacts, and asymptomatic covid-19 infection.

In addition, 22 publications relating to the research questions were collected and reviewed. Data on viral load, shedding, duration, variants, age, gender, and household contacts were reviewed. A careful review of Omicron variants, sublineage, and other main variants was also done to achieve the objective.

3. RESULTS AND DISCUSSION

Isolation policies vital to managing Covid-19 were formulated based on the viral load dynamics and the dose-response model for the virus previously studied before the emergence of Omicron variants [7,8]. These might have influenced the number of studies currently published on the variant. Regardless, current data on the viral load, viral load shedding, the duration of viral load shedding, and several other co-founding factors must be considered to evaluate the transmissibility and management of the variants [8].

The emerging variants of SARS-CoV-2 demonstrate diverse characteristics that major groups worldwide have found to influence the viral transmissibility, viral load, disease severity, lethality, and impact on vaccination or management of the patients. Most of the findings are results of the clinical studies or animal models focusing on linking the viral load to the prognosis and vaccine efficacy, especially among those already vaccinated, intending to compare to those not vaccinated. Therefore, it is understandable that longitudinal data on this topic is limited to viral load dynamics. Fig 1 shows a summary of the vaccine efficacy of Covid-19 in preventing the virus variants infections.

3.1 Variants of Concern (VOC) and Viral Load

A review publication by Silva et al. emphasized that the emerging SARS-CoV-2 Variants of significant concern (VOC) have become a major issue. The role the RNA-dependent RNA polymerase played in introducing mutations in the viral genome, which eventually resulted in the emerging variant, was also highlighted. This was attributed to the average of 0.5 mutations which tend to accumulate over time during the infection cycle of each individual (. As a result of the high transmission rate of the virus over the globe, it can be concluded that the generation of mutations and new variants tends to rise [10].

The eventual result of such is the continuity of the pandemic, given the evolution of the SARS-CoV-2. More than five variants have been identified and categorized according to their transmissibility or severity. Among the identified variants, Omicron (B.1.1.529) was the fifth to be discovered, and it was first reported in Botswana and immediately followed by South Africa, both in November 2021 [10] [12]. To show how dangerous the new variants were to the world, the rate at which they spread to 6 continents within 30 days of the initial discovery. The rapid rate at which those emergent variants spread around the population accumulates widespread attention with Evidence for the transmission or clinical implications [12].

According to the randomized controlled trial study by Marc et al., a relationship between the viral load and studied variants on disease transmission was projected. Considering the current knowledge and findings, it was shown that the VOCs' viral load tends to increase by 2-8 fold but with no major changes in terms of the pattern of contacts across the variants. It was also noted that the viral load level among the variants could be linked with a relative increase in the 'probability of transmission of about 24-58% for household contacts but 15-39% for non-household contacts [14].

Researchers found Omicron to be heavily mutated variants with 30 amino acid substitutions, some deletions involving six residues, and insertions of 3 residues of the spike protein. Those were found to be concentrated around the receptor binding motif. In addition, some insertions were not identified when the variants were first identified but have been later identified among the mutations to be the insertion (ins214EPE) in spike. For the Omicron, scientists have also hypothesized that the identified insertion could easily be acquired as a form of template switching, which entails the genome of a lower pathogenic coronavirus. Especially those coronaviruses found to have the capability to cause the common cold (HcoV-229R). Omicron sublineages have emerged with increasingly higher replication advantages than the previously identified predominant sublineages. The first Omicron identified was the BA.1. sub lineage. Several Omicron sublineages have been found to have replication advantages over the other Delta variants. They also evade the infection and vaccine-induced humeral immunity to a greater extent than what has been noticed with prior variants.

However, in terms of association with severe diseases, the omicron sublineages appear to be associated less. Furthermore, observational data have shown that the risk of severe illness or death with Omicron is lower than with other variants [12].

In a quest to get appropriate data, Van Der Veer et al. implemented infection prevention guidelines for their healthcare workers and necessary testing conducted to evaluate the Ct-value and variant determination via whole genome sequencing with the required genotyping. As a result, the researchers in the longitudinal study found the healthcare workers' viral load dynamics to be different, especially between the three main variants studied (Delta, BA 1, and BA 2 variants).

	Effectiveness at preventing											
	Ancestral		Alpha		Beta		Gamma		Delta		Omicron	
Vaccine	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection
AstraZeneca	94%	63%	94%	63%	94%	69%	94%	69%	94%	69%	71%	36%
CanSino	66%	62%	66%	62%	64%	61%	64%	61%	64%	61%	48%	32%
CoronaVac	50%	47%	50%	47%	49%	46%	49%	46%	49%	46%	37%	24%
Covaxin	78%	73%	78%	73%	76%	72%	76%	72%	76%	72%	57%	38%
Johnson & Johnson	86%	72%	86%	72%	76%	64%	76%	64%	76%	64%	57%	33%
Moderna	97%	92%	97%	92%	97%	91%	97%	91%	97%	91%	73%	48%
Novavax	89%	83%	89%	83%	86%	82%	86%	82%	86%	82%	65%	43%
Pfizer/BioNTech	95%	86%	95%	86%	95%	84%	95%	84%	95%	84%	72%	44%
Sinopharm	73%	68%	73%	68%	71%	67%	71%	67%	71%	67%	53%	35%
Sputnik-V	92%	86%	92%	86%	89%	85%	89%	85%	89%	85%	67%	44%
Other vaccines	75%	70%	75%	70%	73%	69%	73%	69%	73%	69%	55%	36%
Other vaccines (mRNA)	91%	86%	91%	86%	88%	85%	88%	85%	88%	85%	67%	45%

Fig. 1. COVID-19 vaccine efficacy summary [9]

Fig. 2. Daily Covid-19 vaccine doses administered [11]

However, the BA 2 variants were found with the highest viral load within the first 10 days after the initial PCR was collected. However, the infection duration among the three variants appears not to be different. The findings further provide a better understanding of BA 2, especially concerning the transmission and current quarantine rules, which are majorly formulated based on the earlier understanding of the other variants. For instance, quarantine rules are based on viral load found during the infection duration, which targets the individual from the dimension that such an individual will have to be asymptomatic for at least one day during the quarantine days is 5 and 7 days for healthcare workers [15].

To replicate previous findings from earlier studies on Omicron and subsequent sublineages, Dewald et al. [16] determined the viral dynamics of breakthrough omicron infections; both the viral load of the vaccinated and bolstered individuals were measured. The first 3 days of onset of symptoms showed significantly higher viral load Ct 21.76 for the vaccinated and 23.14 for boosted individuals.

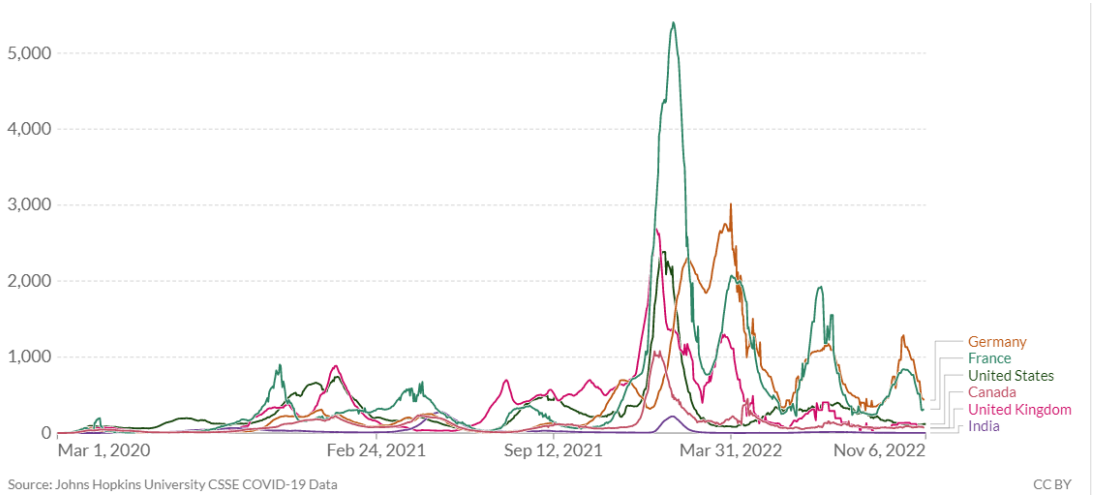

Fig. 3. Daily new confirmed COVID-19 cases per million people [13]

Longitudinal studies were further conducted on the group of patients for 14 days to understand the difference in the viral load trajectory [16]. Findings indicate that booster immunization reduced the detectable viral loads without changing the main viral load dynamics for the period, unlike in vaccinated individuals [16]. However, the findings of this study appear to be different from what Bouton et al. [17] found from a 10-day longitudinal study that has shown that booster vaccination does not have any impact on the virus kinetics but against infection because it reduces transmission [17].

Van Der Veer et al. also identified the various viral loads level of the three studied variants for the five days after the first PCR was done. For instance, BA 2 viral loads [5.7 log10 copies/mL (Ct-value 21] appear to be highest among the three, followed by that of BA1 [4.8 log10 copies/mL (Ct-value 24)] and then Delta variants [4.3 log10 copies/mL(Ct-value 26)]. However, based on their findings, the viral load changes occur with BA 2 having a Ct value of 26, equal to Delta on day 5. The detected loads were considered to represent the intact viral participles in both the vaccinated and unvaccinated persons. Based on the findings, Delta, BA1, and BA 2 were noted to have different viral load dynamics. BA 2 has the highest of the 3 in terms of viral loads. This is considered a strong influencer of the transmission potential despite following the suggested quarantine period [15].

SARS-Cov infections begin in the respiratory tract before spreading to other organs. Therefore, the isolation of viral nucleic acids from those tissues, blood, and body secretions could easily help analyze the systemic spread and determine the severity of the infection [18]. In addition, a constant increased viral load from reviewed data explains the correlations between the increased infectivity and rapid transmission, making it easier to assess viral load from the respiratory tracts to determine the risk of severity [18].

According to scientists, high viral load strongly correlates with elevated cytokine and lymphopenia, which are the main markers of inflammation and portrays a poor prognosis [18]. When comparing the duration of SARS-CoV-2 within the stool, serum, and sputum samples. The virus was found to stay longer in stool samples compared to others. This means stool management must be thoroughly considered while planning to prevent and control the epidemic. However, in the respiratory tissues of a patient with more severe diseases, It was found that the virus could persist longer [12].

Infectious viral load, age, sex and community transmission SAR-CoV infections occur almost anywhere. Therefore, household contact exposure remains a point studied by Singanayagam et al. [19] to understand community transmission and viral load kinetics; The authors focused on the delta variants concerning vaccinated and unvaccinated individuals [19]. Researchers noted peak viral loads do not differ in terms of vaccination status or variant type but tend to increase modestly with age, with a difference of 0.39 in peak $\log_{10}$ viral load per mL between those at the age of 10 years to those at 50 years [19].

Another group of researchers, Puhach et al. [20], tested the correlations between the infectious viral loads, age, and sex among vaccinated and unvaccinated groups. It was evident that no correlation existed between age and infectious viral load among the four groups studied. Similarly, no correlation existed in terms of the infectious viral loads between the male and female patients for those infected with pre-VOC, Delta (fully vaccinated or unvaccinated), or Omicron BA 1, which is fully vaccinated only. This is unlike what was founded by Singanayagam et al. (2022), which observed a modest difference in correlations.

It was also observed that for these delta variants, the viral load had a much faster decline mean rate in fully vaccinated individuals compared to those unvaccinated individuals with pre-alpha (0·69), alpha (0·82), or Delta (0·79) variant infections [19]. Furthermore, the dynamics with regards to the viral growth show that individuals with faster viral load growth tend to have higher peak viral load correlation, i.e., correlation 0.42 [95% credible interval 0.13-0.65] but with a much slower decline rate [-0.44 (-0.67 to -0.18)]). Those results show the impact of vaccination on the viral load, reduced risks of infection of the delta variants and helped in viral clearance.

However, there are still several instances where fully vaccinated individuals with breakthrough infections have peak viral loads similar to that seen in unvaccinated ones, which indicates that such group of individuals can transmit infection within their homes or community is high. Furthermore, the understanding provided by the study by Singanayagam et al. [19] shows that the type of host-virus interactions that occur during the early period of infections strongly influences the entire viral trajectory through the course of infection [19].

The relationship between viral load and transmissibility using epidemiological and clinical data was tested by Kawasuji et al. [21,4]. The index patient (the patient that first transmits the disease to at least another) and the non-index (the patient that causes secondary transmission). High Nasopharyngeal viral load data at the onset provides a better understanding of why some patients easily transmit infections, and others do not. This attributes to the findings regarding the median viral load relating to the initial sample in a symptomatic patient, which is higher than that in asymptomatic patients or higher in adults compared to children [22]. Viral load at onset was higher among the symptomatic patients considered to be index than those non-index patients [22,14]. Regardless of whether symptomatic or asymptomatic, median viral loads maintain a high value in adult patients compared to non-index patients [22].

In addition to those findings, Meyerowitz et al. also noted that having a high viral load associated with the index case needed to be considered vital to super-spreading events, especially during transmission. However, the importance of other specific host factors' contribution to the events is yet unknown. Further study also highlighted how the secondary attack rate is associated with the increased severity of the index case and related symptoms of fever and expectoration, which are known with secondary infections [23].

A study by Darlene Bhavnani et al. found that 77% of the transmission events were associated with the case viral loads of $\geq 1 \times 105$ copies of viral RNA per mL of saliva [24]. In view of the role played by viral shedding in transmission, if cough is a consequence of higher viral loads was questioned by Darlene Bhavnani et al. (if it perpetuates transmission independent of viral load. However, their study still tries to demonstrate the existence of the relationship between the viral load at the time of test and the presence of a cough on the day of exposure or the risk that is present in terms of transmission if a cough occurs on the day of exposure [24]. These major questions are yet to be answered but are still linked to viral loads.

In the study by Cathinka et al. focusing on household transmission, the secondary attack rate was found to be higher in the Alpha variant (78%) when compared to the non-VOC variants (43%). In addition, those cases were found to be associated with higher viral load [25]. Unlike the study by Meyerowitz [16], Cathinka et al. found that children had lower viral loads and were usually more asymptomatic than adults. However, the secondary attack rate was higher among household contacts above 40 years of age (69%) than younger contacts [25].

3.2 Pre-symptomatic Transmission

Tindale et al. (2020) described the rate of novel coronavirus transmission as 40-80%, which usually happens 2-4 days before the onset of symptoms in an infected patient. This type of transmission has made it challenging to manage

the pandemic because of the pre-symptomatic infection's difficulty in containing the spread [5]. In addition, studies have shown viral load to be at a high level during the pre-symptomatic period and then peak during the onset of symptoms but later declines over time [6], [14,18]. According to Tindale et al., most of those transmissions which occur in healthy individuals depict that home lockdown or isolation when an individual shows symptoms is not enough to control the spread of SARS-CoV-2 [26].

Several other measures are needed, such as broad-scale social distancing, which has proven to help prevent asymptomatic transmission of Covid-19. The over-dispersion is usually described as an instance whereby most infected individuals don't transmit at all, and only a few of the infected population remains to be the super-spreader. In another study by Goyal et al. [5], it was described the viral load in the upper respiratory airway to help determine the likelihood of transmission. This was more of a reason because viral load at such upper respiratory tract was found to be highest during the early phase of the disease but later increased downward to the lower respiratory tract (sputum). This also suggests that more viral replications occur at such regions or sites and thus shift to the lower region [23].

The findings by Goyal et al. [5] indicate that exposure to the airway viral load that is shedding determines the probability of transmission of the infection [5]. This other study by Ra et al. [27] indicated that 1/5th of persons without severe symptoms of Covid-19 were asymptomatic. The viral load of the population is comparable to those found in symptomatic patients. It was also highlighted by the notable findings in a large proportion of mildly symptomatic individuals with Covid-19 or those asymptomatic with SARS-CoV-2, which is the existence of persistent positive upper respiratory tract RT-PCR results at follow-up [27]. According to the authors, this asymptomatic population was indicated to exhibit the viral load in the nasopharynx of the patients was comparable to what was found in those with mild symptoms. They emphasized the dangers of such asymptomatic individuals with SARS-CoV-2 infection, which are a major contributor to the ongoing community Covid-19 pandemic.

A study by Puhach et al. [20] quantified the infectious viral load in those infected with Covid-19 during the first five days of showing symptoms utilizing the in-vitro culturability assay in both that are either vaccinated or unvaccinated. The identified individuals are infected with the pre-variant of concern (pre-VOC), including the SARS-CoV-2, Delta, or Omicron BA1 [20]. Unvaccinated individuals with the pre-VOC SARS-CoV-2 were found to have lower infectious viral load than those with Delta variants.

On the other hand, Omicron BA 1 in these breakthrough cases was found to have reduced infectious viral load only in individuals with boosted and not fully vaccinated individuals compared to other groups. Those other groups include the fully vaccinated Omicron BA. 1-infected persons show lower infectious viral load compared to fully vaccinated Delta variants [20]. The implication is that increased infectious viral load determines the infectiousness of the SARS-CoV-2 Omicron BA.1. variants [20]. However, vaccination has its role in lowering the transmission risks, which is pertinent for the public health protection of citizens or healthcare workers [20].

The relationship between the SARS-CoV-2 viral load and infectiousness, which is poorly known in the academic world, was explored by Marc et al. The viral load and probability of infection were analyzed to understand the effect of the viral load [14]. The noted transmission probability was significant, around 48% among the household contacts compared to non-household contacts, especially when the viral load was more significant than 10^{10} copies/mL. Similarly to the viral load level at the symptom onset noted by many scientists, the transmission probability peaked at that exact point [14] but with a mean possibility of a transmission rate of 29%, although with significant individual variations [14].

Another cohort study on the SARS-CoV-2 G614 variant infection found a form of rapid viral load peak occurring at Covid-19 symptom onset, followed by a slower decline but correlated positively with the severity of the symptoms [28]. The longitudinal evaluation of Stankiewicz Karita et al. on the SARS-CoV-2 G614 utilizing the molecular testing mode allows such to serve as the point of reference for future comparison for the emergent viral lineage that could be discovered. This is vital for future clinical trials and the development of public health strategies or policies to contain the virus [28]. It was noted that s with Omicron Omicron Infections are more likely to be vaccinated than those with Delta. However, they were less likely to be admitted or succumb to infection regardless of vaccination

status. A booster dose, however, influences the recovery of infectious virus in the cell culture compared to the fully vaccinated that has no booster or unvaccinated that is infected with delta variants [29].

Apart from the viral load level based on gender or sex which no correlates were found, the relative probability of transmission and the relationship between age and gender is still unclear. However, Meyerowitz et al. [23] found the replication-competent virus to be readily isolated from children compared to adults, especially when the onset of symptoms is not a vital determinant of the viral load [23]. This is simply because the study findings indicate the higher viral load to be more linked with the increased likelihood of infectious viral isolates. About eight days is considered the median after symptoms onset for such isolation to be possible. However, the probability for the isolation declined to about less than 5% post 15.2 days while it further decreased over time.

4. CONCLUSION

At present, reviewed literature has no unified agreement on the implication of quantitative SARS- CoV-2 viral load on the severity of infection. Therefore, the study aims to identify how critical the viral loads and asymptomatic virus status is to SARS-CoV transmission with a focus on Omicron or the importance of the viral load assay to the corresponding clinical outcome of the infection. Several current studies have been critically reviewed to better understand viral load dynamics and transmission probability. However, very few studies focused on Omicron. Emphasis on the VOC's viral load relationship on the transmission probability was considered to differ between household and non-household contacts. The viral loads rose with about 2-8 folds, although the contact pattern has not differed across the variants. Despite the difference in viral load noted by some researchers among the variants and their sublineage, most findings do not note any noticeable difference in terms of the infection duration. Regardless, quarantine rules are still formulated based on the viral load found during the infection duration.

Further studies have explored the impact of vaccination and booster immunizations' on viral loads and implications on the transmission rate. Most of the findings show this to be a positive correlation. However, several exceptions had no relationship between the factors and considered the viral load between unvaccinated and vaccinated to be no significant difference. Based on the reviews, viral load appears to peak at the onset of infection; detected loads represent the intact viral particles regardless of vaccination status. The viral load influences the transmission potential irrespective of the quarantine period, and an increase in viral load positively correlates with the rate of infectivity and rapid transmission regardless of gender. There is a further correlation between the viral load level and index case and the existence of super-spreading events, although not yet agreed upon by a lot of researchers; hence still needs further investigation.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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