ISSN: 2474-3658

Qutub et al. J Infect Dis Epidemiol 2021, 7:227
DOI: 10.23937/2474-3658/1510227
Volume 7 | Issue 9
Open Access

Journal of
Infectious Diseases and Epidemiology

REVIEW ARTICLE

Duration of Viable SARS-Cov-2 Shedding from Respiratory Tract: A Systemic Review of Available Literature

Mohammed Qutub[1], Nezar Bahabri[2], Fahtima Mehdawi[3], Yasser Aldabbagh[4,5*], Mohanna Alhomsy[6], Abdulaziz Alnahdi[3], Majed Fakeeh[3], Abdullah Maghrabi[3] and Meshari Alwagdani[3]

[1]Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia

[2]Chief Medical Officer and Consultant of Infectious Diseases, Doctor Samir Abbas Hospital, Jeddah, Saudi Arabia

[3]Department of Internal Medicine, Doctor Soliman Fakeeh Hospital, Jeddah, Saudi Arabia

[4]Department of Infectious Diseases, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia

[5]Department of Internal Medicine, Al Moosa Specialist Hospital, Al-Ahsa, Saudi Arabia

[6]Department of Critical Care, Suliman Al Habeeb Medical Group, Riyadh, Saudi Arabia

***Corresponding author:** *Yasser Aldabbagh, Department of Internal Medicine, Al Moosa Specialist Hospital, Al-Ahsa, Saudi Arabia; Adult Infectious Diseases Fellow, Department of Infectious Diseases, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia, Tel: 009665-6919-7962*

Abstract

Background: The duration of viable viral shedding is important to define in regards for viral transmission in SARS-CoV-2 infection. In this systemic review the aim was to determine viable viral shedding in SARS-CoV-2 infection.

Methods: In this systemic review we searched databases including Medline and google scholar for research articles published between March 2020 and August 2020. We included case reports, case series, cross sectional, cohort, and randomized control trials that reported duration of shedding of viable SARS-CoV-2 virus. After evaluating the criteria for inclusion 15 articles (2604 patients) were included.

Conclusion: The findings showed that 95% of cases did not showed viable virus after day 16 with median of 11. Viral culture is the gold standard to assess viral viability. This review indicates for certain that repeat testing SARS-CoV-2 viral RNA in patients has no importance in determining infectivity.

Introduction

Historically, six strains of coronaviruses are believed to infect humans, of which four strain where identified from upper respiratory tract infection from patient with common cold [1], the other two, are associated with more severe disease and mortality including sever acute respiratory syndrome (SARS-CoV) and Middle east respiratory syndrome (MERS-CoV) [2], the seventh coronavirus was identified as a cause of pneumonia outbreak in Wuhan, China in December 2019 [3], the later three are believed to be zoonotic in origin although the intermediate carrier of sever acute respiratory syndrome coronavirus - 2 (SARS-CoV-2) is not yet precisely known [4].

The main route for SARS-CoV-2 transmission is by close contact and respiratory droplet allowing high rate of infectivity, which pose a real challenge on health care systems that necessitate the need of contact tracing and testing. Real Time polymerase chain reaction (RT-PCR) have become the standard of SARS-CoV-2 diagnosis because of its high sensitivity and specificity [5-8].

SARS-CoV-2 RNA positivity by RT-PCR have been reported up 12 weeks, but RT-PCR positivity does not represent the presence of viable virus [9]. Confirmation

Citation: Qutub M, Bahabri N, Mehdawi F, Aldabbagh Y, Alhomsy M, et al. (2021) Duration of Viable SARS-Cov-2 Shedding from Respiratory Tract: A Systemic Review of Available Literature. J Infect Dis Epidemiol 7:227. doi.org/10.23937/2474-3658/1510227

Accepted: September 15, 2021: **Published:** September 17, 2021

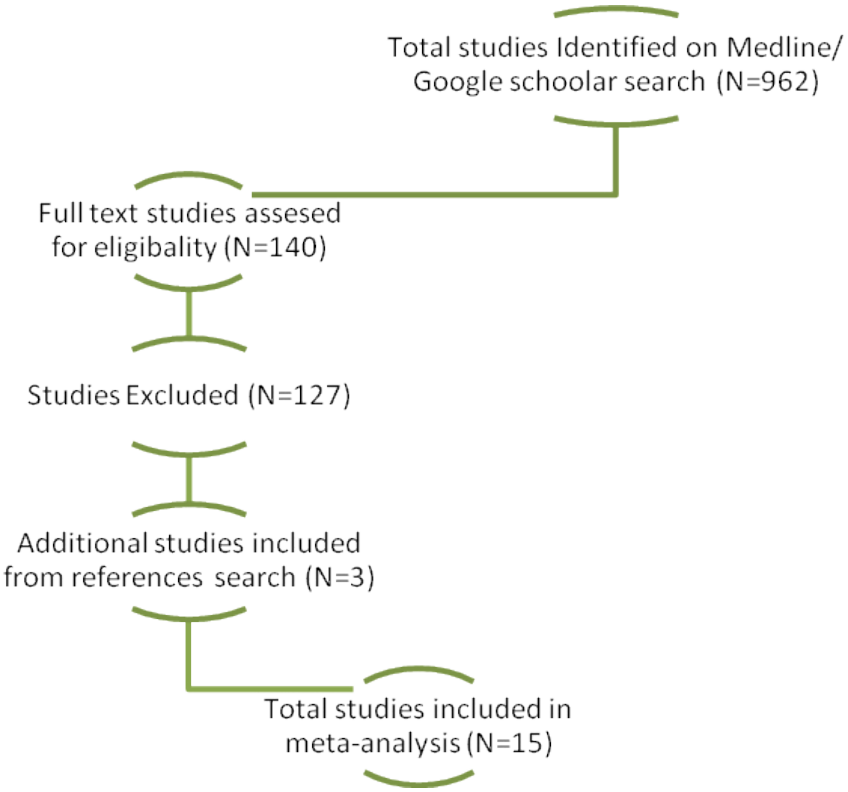

Figure 1: Prisma Algorithm for database search and article selection.

of virus replication and infectivity require viral culture, which is not practical in acute setting as the virus require prolonged time to be isolated and specific laboratory setting with biosafety level of 3 or more [6].

Based on available published literature, the center of disease control and prevention (CDC) stated that discontinuing isolation can be considered after day 10 of symptoms onset, which can be extended to 20 days for severe cases or immunocompromised individual, awaiting more solid evidence regarding replication-competent virus shedding, which is still an area of debate [10,11].

Method

Search strategy and selection criteria

We conducted a comprehensive search on both Medline and google scholar database up to August 2020, using keywords "COVID-19" Or "SARS-CoV-2" Or "Coronavirus" combined with "Culture" or "Virus Isolation" with the use of keywords' Medical Subject Heading (MESH) And truncation, total studies screened where 962, of which 140 full text studies were assessed for eligibility.

The total studies included in meta analysis where 15 after exclusion of 127 articles with three additional studies included from references search. The main reason for exclusion includes if the study method did not include viral culture, if the purpose of viral isolation was for sequencing, genotyping or phenotyping purpose, if the study reported viral culture form non-respiratory body fluid, or if the last day of successful isolation was not clearly mentioned in the study (Figure 1).

Data analysis

We reviewed the final articles to extract the following information from each: First Author, setting, name of the journal, date of article first available online (month during 2020), study sample size, number of cases with successful viral isolation, last day of positive culture, type of sample, cycle threshold Value (CTv) and viral load (Table 1), data were analyzed using SPSS. Median, mean difference, confidence interval of the mean difference and standard deviation were calculated using Anova-T test.

Results

The systemic search included 962 possible relevant articles. After evaluating the criteria for inclusion 15 articles (2604 patients) were included (Table 1). Of the 15 articles included, 3 were done in China [12,13,25], 7 were done in Europe [14,16,17,20,22-24,26], 1 in USA [15], 1 in Canada [19], 1 in United Kingdom [26], 1 in Taiwan [21], and 1 in Australia [18]. Regarding patient setting, 10 studies included hospitalized patient [12-16,20-24]. None of the studies included children.

In regard to type of samples used when assessing viral culture 10 studies used a combination of samples from nasopharyngeal, oropharyngeal, and/or sputum; 4 studies tested samples through nasopharyngeal swab alone; and 1 study tested samples directly from saliva [12]. One study was able to isolate virus from 16% of

DOI: 10.23937/2474-3658/1510227

Table 1: Selected studies and their characteristics.

S.No	Study author(S), Setting	Journal, Available Online (2020)	Study Sample size	Successful Viral isolation						
				Number of patient(s)	Last day	Type of sample	CTv		Viral Load (X Log 10)	
							Lowest	Highest	Lowest	Highest
1	Kelvin Kai-Wang To, et al. Hong Kong, China [12]	Clinical infectious disease, February	12	3	7	Saliva	NSR	NSR	NSR	NSR
2	Francois-Xavier Lescure, et al. Wuhan, Hubei Province, China [13]	Lancet Infectious Disease, March	6	2	2	NP	19.3	26.5	4	8
3	Roman Wölfel, et al. Munich, Germany [14]	Nature, April	16	9	8	NP OP Sputum	NSR	NSR	6	10
4	M.M. Arons, et al. Washington, United states of America [15]	The New England Journal of Medicine, April	89	30	9	NP OP	13.7	37.9	NSR	NSR
5	P. Gautret, et al. Marseille, France [16]	Travel Medicine and Infectious Disease, April	80	46	9	NP	14	33	NSR	NSR
6	Bernard La Scola, et al. Marseille, France [17]	European Journal of Clinical Microbiology & Infectious Diseases, April	183	129	8	NP Sputum	13	34	NSR	NSR
7	H. Rahman, et al. Westmead, Australia [18]	Journal of Clinical Virology, April	52	5	9	NP OP Sputum	19.9	35.2	NSR	NSR
8	Jared Bullard, et al. Winnipeg, Canada [19]	Clinical Infectious Diseases, May	90	26	8	NP ETT	16	18	NSR	NSR
9	Matthieu Million, et al. Marseille, France [20]	Travel Medicine and Infectious Disease, May	1061	204	10	NP	14.8	34	NSR	NSR
10	Wang-Da Liu, et al. Taipei City, Taiwan [21]	Journal of Infection, May	1	1	18	OP Sputum	NSR	NSR	NSR	NSR
11	Jean-Christophe Lagier, et. al. Marseille, France [22]	Travel Medicine and Infectious Disease, June	3737	1908	10	NP OP Sputum	NSR	NSR	NSR	NSR
12	Jeroen J.A. van Kampen et al. Rotterdam, The Netherlands [23]	MedRxiv preprint, June	129	33	20	NP ETT	NSR	NSR	6.24	10
13	M Dolores, et al. Madrid, spain [24]	Medrevix preprint, June	106	59	32	NP	21.1	39.3	NSR	NSR

ISSN: 2474-3658

14	Ranawaka A.P.M, et al. Hong Kong, china [25]	Emergent Infectious Disease, July	68	16	8	NP OP	NSR	NSR	5	10
15	Anika Singanayagam, et al, Colindale, United Kingdom [26]	Euro Surveillance, August	324	133	12	NP OP	17.5	41.8	NSR	NSR

CTv: Cycle Threshold Value; NSR: Not Specifically Reported; NP: Nasopharyngeal Swab Or Aspirate (Nas); OP: Oropharyngeal Swab or Wash (Throat); ETT: Endotracheal Tube Specimen.

swabs compared to 83% isolation from sputum samples [14].

In respect to the technique in culturing the virus, viral culturing was done using vero-cells in 8 of the studies [14,15,17,19,21,23,24,26]. In regard to patient presentation and viral isolation, 5 studies provided duration of viral viability categorized by illness severity, One study showed that presymptomatic samples were at least as likely to be culture positive as samples taken during symptomatic phases [26], One study demonstrated viability of virus in comparison to symptom onset, and there was no growth in samples from patients with symptom onset for more than 8 days [19], One case report detected viable virus up to 18 days from symptom onset in a patient with severe disease [21], Another study detected viable virus up to 8 days from symptom onset in sever disease, and ≤ 5% for isolating infectious SARS-CoV-2 when the duration of symptoms was 15.2 days [23], While another study showed that patients with mild disease viral viability lasted up to 10 days, while in severe disease virus can remain viable for up to 32 days [24].

In relation to type of treatment used 4 studies provided duration of viral viability in relation to hydroxychloroquine and azithromycin. The number of patients with positive culture decreased, as early as three days with administration of azithromycin and hydroxychloroquine [16]. 1 study provided comparison of isolation in relation to remedisivir, which showed decrease in trend of viral isolation with administration of remedisivir [13].

In relation to neutralizing antibodies one study demonstrated a serum neutralizing antibody titer of at least 1:80 was associated with non-viable virus [23].

When looking at the relation of CTv and cultivated virus**,** the corresponding CTv to culturable virus ranged between 14.30 and 38.83 with mean of 16.59 to 33.30 and median of 16.00 to 34.00, the viral load ranged between 3.68 and 11.09 × log 10 with mean of 5.31 to 9.5 × log 10, median of 5.50 to 10.00 × log 10 and overall median of 7.12 (Table 2).

In respect of last day of cultivated virus most of the data retrieved from systematic review of the above-mentioned articles showed that the last day of successful viral isolation ranged somewhere between 7.37 to 15.30 days (95% confidence interval) with mean of 11.33 days and median of 9 days.

Discussion

This systemic review provides data on the understanding of SARS-CoV-2 infectivity. The findings show that 95% of samples are no longer viable after day 16, with median 9 days, and with a mean of 11.3 days. These findings correlate with the same suggestions made from the Center of Disease Control, that in 88%

Table 2: Median, mean difference, confidence interval of the difference and standard deviation of studies variable.

	Median	Mean Difference	95% Confidence Interval of the Difference		Standard deviation
			Lower	Upper	
Last day of successful viral isolation	9.00	11.33	7.37	15.30	7.16
Cycle Threshold Value (CTv)	20.50	24.94	19.91	29.98	10.12
• Lowest	16.00	16.59	14.30	18.88	2.98
• Highest	34.00	33.30	27.77	38.83	7.20
Viral Load	7.12	7.41	5.38	9.43	2.43
• Lowest	5.50	5.31	3.68	6.94	1.03
• Highest	10.00	9.50	7.91	11.09	1.00

to 95% of SARS-CoV-2 cases duration of infectiousness lasts up to 10-15 days for mild to moderate and severe cases, respectively [10,11].

To date, the diagnosis of COVID-19 has relied on the detection of SARS-CoV-2 through molecular detection [5-8]. While this method is both rapid and highly sensitive, there are important limitations. A few of the studies showed that patients with SARS-CoV-2 continue to have prolonged viral shedding, one study showed the presence of viral RNA in respiratory samples up to 60 days, but no live virus was cultivable beyond 18 days [22]. The use of RT-PCR as a follow-up method for SARS-CoV-2 infection has led to infer misleading information regarding the duration of infectivity of patients. However, the ability to use viral culture to determine infectivity remains challenging due unavailable of resources and the labor-intensive nature.

There was also an unpredictability when cultivating virus from certain samples. It was seen that nasopharyngeal swab fluid might be less representative than sputum samples when trying to culture the virus, despite high viral loads [17,21]. Similarly, viral isolation from stool was not successful, even though viral RNA may remain positive in stool for up to 25 days [27], Indicating that some types of samples are less sensitive for the cultivation of virus.

A relationship is apparent between the lower CTv threshold and cultivated SARS-CoV-2 virus [17], with cutoff of 34 based on most of the published articles [13,16,17,19,20]. In this review the analysis showed that 95% of the viable samples have CTv less than 38 and confirmed a median CTv of 34. Based on these findings infection prevention and control guidelines may take into account that CTv equal or above 34 may be safely discharged and no longer require isolation.

SARS-CoV-2 viral load is believed to peak at the end of first week in mild to moderate cases and remain high or peak again in severe diseases in the second week [28]. There is variability in the duration of shedding of viable virus in patients with severe disease, patients who are immunocompromised, and recently even in patient who received corticosteroid [23], Viable virus can be frequently demonstrated during prolonged periods up to 4 weeks in patients with severe SARS-CoV-2 infection but Some evidence suggests that the CTv is insufficient to identify samples with viable virus in severe SARS-CoV-2 infection, and viral replication is best demonstrated by viral culture [24].

There were several limitations in this systemic review. One limitation is the attribution to that most of studies included includes heterogenous data in regards of diseases symptomatology and severity, another point that some studies did not specifically report the relationship between CTv or viral load but correlated rather to RT-PCR. Despite a huge effort done from the start of the pandemic, further studies regarding SARS-CoV-2 transmutability dynamics are needed, especially in post-vaccination era.

Conclusion

With SARS-COv-2 infection in respect of symptomatology and severity, more than 95% of cases did not showed viable virus after day 16 with median of 11. Viral culture is the gold standard to assess viral viability, however, remains challenging due to unavailable resources and the labor-intensive nature. This review indicates for certain that repeat testing SARS-CoV-2 viral RNA in patients has no importance in determining infectivity and emphasize that CTv and viral load have wide range of cutoff in some settings making the sole use in determining infectivity and viable virus may be unreliable.

Acknowledgment

Not applicable.

Conflict of Interests

The authors declare that they have no conflicts of interests.

Funding Information

This study was not financially funded by any governmental, medical or pharmaceutical agencies.

References

1. Su S, Wong G, Shi W, Liu J, Lai ACK, et al. (2016) Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol 24: 490-502.

2. Cui J, Li F, Shi Z-L (2019) Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 17: 181-192.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, et al. (2020) A novel coronavirus from patients with pneumonia in china, 2019. N Engl J Med 382: 727-733.
4. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (2020) The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)-China, 2020. China CDC Weekly 2: 113-122.
5. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC (2020) Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. JAMA 324: 782-793.
6. Li C, Zhao C, Bao J, Tang B, Wang Y, et al. (2020) Laboratory diagnosis of coronavirus disease-2019 (COVID-19). Clinica Chimica Acta 510: 35-46.
7. Steinbrook R (2020) Contact tracing, testing, and control of covid-19-learning from taiwan. JAMA Intern Med 180: 1163.
8. Shen M, Zhou Y, Ye J, Al-Maskri AAA, Kang Y, et al. (2020) Recent advances and perspectives of nucleic acid detection for coronavirus. J Pharm Anal 10: 97-101.
9. Sun J, Xiao J, Sun R, Tang X, Liang C, et al. (2020) Prolonged persistence of SARS-CoV-2 RNA in body fluids. Emerg Infect Dis 26: 1834-1838.
10. CDC (2021) Interim guidance on ending isolation and precautions for adults with COVID-19. Centers for Disease Control and Prevention.
11. CDC (2021) Discontinuation of Transmission-Based Precautions and Disposition of Patients with SARS-CoV-2 Infection in Healthcare Settings. Centers for Disease Control and Prevention.
12. To KK-W, Tsang OT-Y, Yip CC-Y, Chan K-H, Wu T-C, et al. (2020) Consistent detection of 2019 novel coronavirus in saliva. Clin Infect Dis 71: 841-843.
13. Lescure F-X, Bouadma L, Nguyen D, Parisey M, Wicky P-H, et al. (2020) Clinical and virological data of the first cases of COVID-19 in Europe: A case series. Lancet Infect Dis 20: 697-706.
14. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, et al. (2020) Virological assessment of hospitalized patients with COVID-2019. Nature 581: 465-469.
15. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, et al. (2020) Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. N Engl J Med 382: 2081-2090.
16. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, et al. (2020) Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. Travel Med Infect Dis 34: 101663.
17. La Scola B, Le Bideau M, Andreani J, Hoang VT, Grimaldier C, et al. (2020) Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. Eur J Clin Microbiol Infect Dis 39: 1059-1061.
18. Rahman H, Carter I, Basile K, Donovan L, Kumar S, et al. (2020) Interpret with caution: An evaluation of the commercial Aus Diagnostics versus in-house developed assays for the detection of SARS-CoV-2 virus. J Clin Virol 127: 104374.
19. Bullard J, Dust K, Funk D, Strong JE, Alexander D, et al. (2020) Predicting infectious severe acute respiratory syndrome coronavirus 2 from diagnostic samples. Clin Infect Dis 71: 2663-2666.
20. Million M, Lagier J-C, Gautret P, Colson P, Fournier P-E, et al. (2020) Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis 35: 101738.
21. Liu W-D, Chang S-Y, Wang J-T, Tsai M-J, Hung C-C, et al. (2020) Prolonged virus shedding even after seroconversion in a patient with COVID-19. J Infect 81: 318-356.
22. Lagier J-C, Million M, Gautret P, Colson P, Cortaredona S, et al. (2020) Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. Travel Med Infect Dis 36: 101791.
23. Kampen JJA van, Vijver DAMC van de, Fraaij PLA, Haagmans BL, Lamers MM, et al. (2020) Shedding of infectious virus in hospitalized patients with coronavirus disease-2019 (COVID-19): Duration and key determinants. medRxiv.
24. Folgueira MD, Luczkowiak J, Lasala F, Perez-Rivilla A, Delgado R (2020) Persistent SARS-CoV-2 replication in severe COVID-19. medRxiv.
25. Perera RAPM, Tso E, Tsang OTY, Tsang DNC, Fung K, et al. (2020) SARS-CoV-2 virus culture and subgenomicrna for respiratory specimens from patients with mild coronavirus disease. Emerg Infect Dis 26: 2701-2704.
26. Singanayagam A, Patel M, Charlett A, Bernal JL, Saliba V, et al. (2020) Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro Surveill 25: 2001483.
27. Lui G, Ling L, Lai CK, Tso EYk, Fung KSc, et al. (2020) Viral dynamics of SARS-CoV-2 across a spectrum of disease severity in COVID-19. J Infect 81: 318-356.
28. Wang X, Zheng J, Guo L, Yao H, Wang L, et al. (2020) Fecal viral shedding in COVID-19 patients: Clinical significance, viral load dynamics and survival analysis. Virus Res 289: 198147.