Original Article

Evaluation of the potential for transmission of coronavirus disease via saliva: a systematic review and meta-analysis

Ali Amiri[1,*] (iD), Pantea Moradinejad[2] (iD), Navid Nasrabadi[3] (iD), Marzieh Ghasemi Vojoodi[4] (iD)

[1] Department of Orthodontics, College of Stomatology, The First Affiliated Stomatological Hospital, Xi'an Jiaotong University, Xi'an 710004, PR China

[2] Iranian Association of Periodontology, Tehran, Iran

[3] Department of Endodontics, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[4] School of Dentistry, Kermanshah University of Medical Sciences, Kermanshah, Iran

Corresponding author:
Ali Amiri
Department of Orthodontics, College of Stomatology, The First Affiliated Stomatological Hospital, Xi'an Jiaotong University, Xi'an 710004, PR China
Tell: +86-2982655450
Email: draliamiri2020@gmail.com

Aim: One of the main factors that play a pivotal role in the transmission of COVID-19 from human to human is saliva; according to the subject's importance, the present study aimed to evaluate the potential of transmission via the saliva of coronavirus disease. **Methods:** PubMed, ISI, Embase, Scopus, Medicine have been used until September 2020 to search for articles. Therefore, EndNote X9 used to manage electronic resources. A 95% confidence interval (CI) effect size, fixed effect model, Inverse-variance methods have been calculated. The positive rate of SARS-CoV2 assessed with meta analysis. To deal with potential heterogeneity, random effects were used, and I2 showed heterogeneity. I^2 values above 50% signified moderate-to-high heterogeneity. The Meta-analysis has been evaluated with Stata/MP v.16 (the fastest version of Stata) statistical software. **Results:** According to the study's purpose, in the initial search with keywords, 19 articles were found, the full text of 3 studies was reviewed, and finally, three studies were selected. The positive rate of SARS-CoV2 was 86% (86%; 95% CI 67 %-100%). **Conclusion:** saliva can be a non-invasive specimen type for diagnosis of COVID-19. Dentists should be aware that saliva plays a major role in the transmission of COVID-19 from human to human, and failure to follow prevention protocols can contaminate them.

Keywords: COVID-19. Dental health services. Saliva.

Introduction

In the current context of the world, since the advent of COVID-19 in December 2019 in Wuhan, China[1], the disease has become a major global health concern. On February 11, 2020, The World Health Organization (WHO) has declared a new title for the 2019-nCoV: Corona Virus Disease (COVID-19) epidemic infection[2]. According to the WHO, the global mortality rate over time was estimated at 5.7% using a 14-day estimate[3]. Early studies reported transmitted from animals to humans, but studies have illustrated human-to-human transmission of the covid-19 through droplets or direct contact[4,5]. So far, the 2019-nCoV has affected more than 43,150,456 reported cases, according to a new report by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (October 26, 2020). In the sixth edition of the COVID-19 treatment regimen (Trial Implementation)[6], it was reported that the possible routes of transmission of COVID-19 are direct contact and transmission through respiratory particles. In a closed environment, aerosols may be transferred, and more people are at risk for aerosol transmission[7].

COVID-19 transmission is expected to be seen during contact during dental clinical procedures with droplets and aerosols; aerosols can pose potential risks to the dentist and reciprocally to the patient. Dentists need to evaluate effective strategies to prevent COVID-19 infection during the aerosol production process. One of the main factors that play a pivotal role in the transmission of COVID-19 from human to human is saliva. According to the subject's importance, the present study aimed to evaluate the effect size of 2019-nCoV and the potential of transmission via the saliva of coronavirus disease.

Materials and Methods

PubMed, ISI, Embase, Scopus, Medicine have been used until September 2020 to search for articles. Therefore, EndNote X9 is used to manage electronic resources. PubMed search was conducted using mesh terms:

("COVID-19 vaccine" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept]) AND ("Saliva"[Mesh] OR "saliva-interacting cell wall protein, Streptococcus" [Supplementary Concept] OR "saliva natura" [Supplementary Concept])) AND "Dental Health Services"[Mesh].

The present study answers the following question:

What is the probability of transmitting the coronavirus disease through saliva?

Inclusion criteria included were randomized controlled trials studies, controlled clinical trials, In vitro studies, case studies, case reports, and prospective and retrospective cohort studies, Only studies have reported the transmission of COVID-19 through saliva and aliva specimens were collected at 0−14 days after hospitalization. Review studies were excluded from the present article.

Data extraction methods

Data extracted from the studies were included sample size, study, study design. New-castle-Ottawa Scale (NOS) used to assessed quality of the cohort studies, The scale scores range from 0 (lowest grade) to 6 (highest grade). Effect size with 95% confidence interval (CI), fixed effect model, Inverse-variance methods were calculated. To deal with potential heterogeneity, random effects were used, and I2 showed heterogeneity. I^2 values above 50% signified moderate-to-high heterogeneity. The Meta-analysis has been evaluated with Stata/MP v.16 (the fastest version of Stata) statistical software.

Results

According to the study's purpose, in the initial search with keywords, 19 articles were found. In the first step of selecting studies, 14 studies were selected to review the abstracts. Then, studies that did not meet the inclusion criteria were excluded from the study. In the second step, the full text of the three studies was reviewed. Finally, three studies were selected (Figure1).
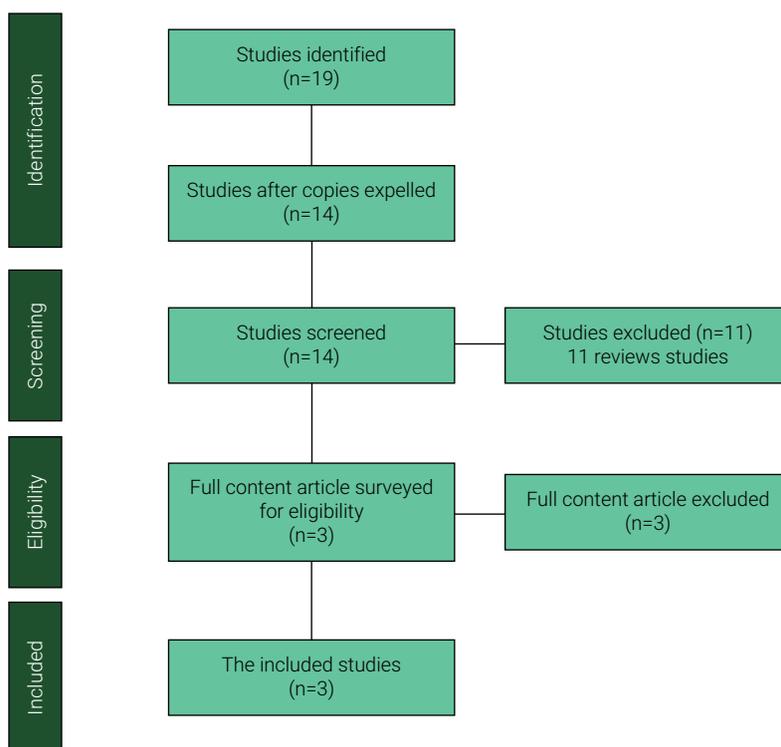

Figure 1. Study Attrition

Characteristics

The sample size total was 74 patients with 62 years mean of age between 37-75 years. Saliva specimens in To et al. (2020)[8], Meng et al.[9] (2020) and Williams et al. (2020)[10]

were 2 , 4 and 6 days, respectively. Overall, 11/12, 20/23, and 33/39 patients detected in saliva in To et al. (2020)[8], Meng et al.[9] (2020) and Williams et al. (2020)[10], respectively.

The positive rate of SARS-CoV2

The effect size of studies included in the present systematic review and meta-analysis was 86% (86%; 95% CI 69 %-100%). This result has shown saliva's potential to be a non-invasive type of specimen for 2019-nCoV diagnosis and viral load monitoring.

Table 1. Details of selected studies according to inclusion criteria

Study. Years	Study disegn	Place	Sample size	Mean/range of age (years)	Patient specimens	Saliva specimens*	SARS-CoV-2 detected in saliva
To et al., 2020[8]	Cohort	public Health Laboratory Services Branch in Hong Kong	12 Female:5 Male: 7	62.5/37 to 75	2 mL Saliva / cough sterile	Two days 0-7 days	11/12
Meng et al., 2020[9]	Cohort	Hospital of Stomatology, Wuhan University	23 Female:10 Male: 13	62 / 37−75	-----	Four days 0-13 days	20/23
Williams et al., 2020[10]	Cohort	Royal Melbourne Hospital	39	NR	NR	six days 0-14 days	33/39

* Saliva specimens were collected at a median of days after hospitalization

SARS-CoV-2 detected in saliva

Study		Effect Size with 95% CI	Weight (%)
To et al.,2020		0.91 [0.56, 1.26]	25.52
Meng et al.,2020		0.86 [0.55, 1.17]	32.30
Williams et al.,2020		0.84 [0.57, 1.11]	42.18
Overall		0.86 [0.69, 1.04]	

Heterogeneity: I^2 = 0.00%, H^2 = 0.05

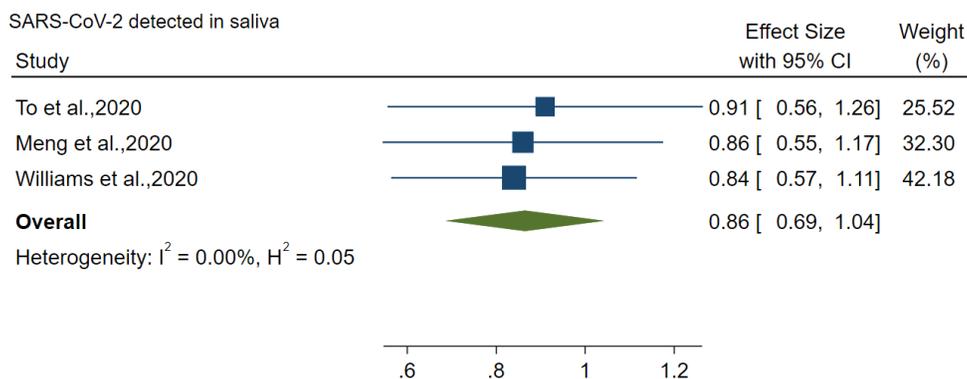.6 .8 1 1.2

Fixed-effects inverse-variance model

Figure 2. Forest plot showed an effect size of 2019-nCoV was detected in the initial saliva specimens.

Discussion

The most common symptoms are: fever, tiredness, cough, aches and pains, sore throat, conjunctivitis, diarrhea, loss of taste or smell, headache, skin rash, or finger or toe discoloration are less common symptoms. And most importantly, there are Severe symptoms require special attention, which includes: shortness of breath

or difficulty breathing, chest pain or pressure, loss of speech or movement[11,12]. Although coronavirus infection is mild, severe acute respiratory syndrome coronavirus (SARS-CoV) leads to high mortality rates[13]. It should be noted that some patients are carriers and have only mild symptoms (carriers). It takes an average of 5-6 days for a person to get the virus to show symptoms, but it can take up to 14 days. Some of the characteristics of the virus are still unknown due to the novelty of the virus. COVID-19 has recently been reported to be detected in infected patients' saliva, so its spread through saliva is possible. Casaroto et al.[13], 2020, evaluate the effect of cooling water temperatures on changes in pulp chamber temperatures and showed when using a high-speed handpiece, too much heat is generated, which should use a water coolant. Water coolant can create aerosols, and when combined with saliva in the oral cavity, bio-aerosols are formed. Bio-aerosols originate from various sources and may be hazardous to healthcare workers and patients due to their potential pathogenic nature. Zemouri et al. [14], 2017, in a review reported that 38 types of microorganisms found in the dental clinic air, and for both patients and healthcare workers, all aerosols may be hazardous. Several studies show that the transmission of Covid-19 occurs mostly through oral droplets[15-18].

Studies in the field of oral dentistry provide an opportunity to determine if a diagnosis of non-invasive saliva for COVID-19 could assist detect such viruses and reduce their spread. In China, researchers can develop unique PCR tests focusing on COVID-19 diagnosis by examining viral genome sequence data from international GenBank databases[12,19]. To date, the routes of transmission of COVID-19 have not been fully elucidated; however, human-to-human transmission has been confirmed. Throat samples and blood tests can be used to diagnose the virus[20-22].

Potential routes of transmission of COVID-19 include Cough, sneezing, and aerosols produced during the clinical process and even talking. As a result, it can be said that the source of the droplets can be the throat or pharyngeal cavity, which are generally associated with saliva[23]. Small droplets can remain suspended in the air, and larger droplets can help transmit the virus. It has also been reported that transmission by contaminated blood may occur. Dentists may carelessly or unknowingly care for carrier patients[21,24]. Studies have shown that about 29% of patients with COVID-19 are health care workers[25].

Because the airborne particles and aerosols produced during the dental process are inhaled, COVID-19 transmission occurs rapidly in dentistry, especially in dentists who directly contact the patient[26]. As a result, dentists should be aware of prevention methods and adopt preventive strategies. According to the mentioned transmission routes, COVID-19 can spread to dental offices. As a result, hands should be washed regularly, all equipment and surfaces should be disinfected regularly, and personal protective equipment and preferably disposable items should be used. Aerosol droplets are produced when coughing, laughing, talking, or sneezing. Aerosol droplets are droplets smaller than five μm diameter and larger droplets larger than 5 μm diameter. Small droplets settle faster than larger droplets and stay in the air longer, while large droplets fall to the ground quickly and can be transferred to another person in less time[27]. Otter et al. [28], 2013 evaluate the evidence that contaminated surfaces contribute to the transmission of pathogens

in hospitals; the result showed contaminated surfaces contribute to transmission. Baghizadeh Fini. [29], 2020, examine the routes of respiratory virus transmission among humans; the result showed respiratory viruses, droplets, or aerosols are transmitted via contact.

One way to diagnose COVID-19 is to use salivary diagnosis platforms, which may detect saliva infection in some virus strains for up to 29 days[30,31]. In this type of test, because the person has close contact with infected patients to collect the sample, there may be a transmission risk.

The COVID-19 virus is present in saliva in three different pathways:

1. Lower or upper respiratory tract presence

2. Enter with fluids[21]

3. Minor or major salivary gland infection[21]

In an animal study, it was shown that salivary gland cells could be the main source of COVID-19[22]. Further studies on saliva and its effect on the transmission of the virus should be performed to confirm these findings. To suggest more effective follow-up methods, especially in dentists who perform aerosol production methods themselves.

The current systematic review and meta-analysis have aimed to evaluate the potential of transmission via the saliva of coronavirus disease. Present meta-analysis showed overall 86% patients (86%; 95% CI 67 %-100%) had SARS-CoV-2 detected in saliva. Personal protective equipment and hand cleanliness practices, Personal protective equipment (PPE), preprocedural mouth rinse, Single-Use (Disposable), periapical radiography. Cone-beam computed tomography (CBCT) and periapical (PA), Rubber dam, sodium hypochlorite for root canal irrigation, disinfect inanimate surfaces, Ultrasonic scaling instruments and, airborne Infection Isolation.

The advantages of using saliva samples in the diagnosis of 2019-nCoV can be the following:

1. Saliva samples can be easily prepared by the patient without any invasive methods.

2. The use of saliva samples can reduce the risk of nosocomial transmission 2019-nCoV.

3. Saliva samples can be collected in outpatient or community clinics.

4. In an environment where large numbers of people need screening, saliva is a non-invasive sample.

5. Using saliva samples reduces the waiting time to collect samples, so results will be available faster. This method is especially important in crowded hospitals where the number of available staff is limited.

The results of the present systematic review and meta-analysis study show that saliva can be a non-invasive type of specimen used to diagnose COVID-19. Saliva can be easily obtained from the patient, saliva use also reduces the risk of transmission, and

saliva samples can be useful for patients who cannot be PCRed. Salivary transmission is also possible and should be observed in dental clinics so that patients are not exposed to saliva. Finally, all dentists should be aware that saliva plays a major role in the transmission of COVID-19 from human to human, and failure to follow prevention protocols can contaminate them.

References

1. Wei FF, Moradkhani A, Hemmati Hezaveh H, Miraboutalebi SA, Salehi L. Evaluating the treatment with favipiravir in patients infected by COVID-19: a systematic review and meta-analysis. Int J Sci Res Dent Med Sci. 2020;2(3):87-91. doi: 10.30485/IJSRDMS.2020.241494.1079.

2. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020 May;46(5):854-87. https://doi.org/10.1007/s00134-020-06022-5.

3. Gaye B, Fanidi A, Jouven X. Denominator matters in estimating COVID-19 mortality rates. Eur Heart J. 2020 Oct 1;41(37):3500. doi: 10.1093/eurheartj/ehaa282.

4. Aponte Mendez M, Rivera Marval EK, Talebzade Toranji M, Amini F, Casaroto AR. Dental care for patients during the Covid-19 outbreak: a literature review. Int J Sci Res Dent Med Sci. 2020;2(2):42-5. doi:10.30485/IJSRDMS.2020.232096.1058.

5. Borges do Nascimento IJ, Cacic N, Abdulazeem HM, von Groote TC, Jayarajah U, Weerasekara I, et al. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. J Clin Med. 2020 Mar 30;9(4):941. doi: 10.3390/jcm9040941.

6. China NHC. [New Coronavirus pneumonia prevention and control protocol]. 5. ed. National Health Commission of the People's Republic of China; 2020 [cited 2020 Nov 8]. Available from: http://www.nhc.gov.cn/xcs/fkdt/202002/e84bd30142ab4d8982326326e4db22ea.shtml. Chinese

7. Wang J, Du G. COVID-19 may transmit through aerosol. Ir J Med Sci. 2020 Nov;189(4):1143-4. doi: 10.1007/s11845-020-02218-2.

8. To KK, Tsang OT, Yip CC, Chan KH, Wu TC, Chan JM, et al. Consistent detection of 2019 novel coronavirus in saliva. Clin Infect Dis. 2020 Jul;71(15):841-3. doi: 10.1093/cid/ciaa149.

9. Meng L, Hua F, Bian Z. Coronavirus disease 2019 (COVID-19): emerging and future challenges for dental and oral medicine. J Dent Res. 2020 May;99(5):481-7. doi: 10.1177/0022034520914246.

10. Williams E, Bond K, Zhang B, Putland M, Williamson DA. Saliva as a non-invasive specimen for detection of SARS-CoV-2. J Clin Microbiol. 2020 Jul 23;58(8):e00776-20. doi: 10.1128/JCM.00776-20.

11. Chang D, Lin M, Wei L, Xie L, Zhu G, Cruz CS, et al. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. JAMA. 2020 Mar 17;323(11):1092-3. doi: 10.1001/jama.2020.1623.

12. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5.

13. Casaroto AR, Jamali J, Amini F, Talebzade Toranji M, Kayasöken G. Evaluation epidemiology, symptoms, and routes of COVID-19 for Dental care: a literature review. Int J Sci Res Dent Med Sci.2020;2(2):37-41. doi: 10.30485/IJSRDMS.2020.231680.1056.

14. Zemouri C, de Soet H, Crielaard W, Laheij A. A scoping review on bio-aerosols in healthcare and the dental environment. PloS one. 2017;12(5):e0178007. doi.:10.1371/journal.pone.0178007.

15. Bahl P, Doolan C, de Silva C, Chughtai AA, Bourouiba L, MacIntyre CR. Airborne or droplet precautions for health workers treating COVID-19? J Infect Dis. 2020 Apr 16;jiaa189. doi: 10.1093/infdis/jiaa189.

16. Morawska L, Tang JW, Bahnfleth W, Bluyssen PM, Boerstra A, Buonanno G, et al. How can airborne transmission of COVID-19 indoors be minimised? Environ Int. 2020 Sep;142:105832. doi: 10.1016/j.envint.2020.105832.

17. Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal–oral transmission. Gastroenterology. 2020 May;158(6):1518-9. doi: 10.1053/j.gastro.2020.02.054.

18. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr. 2020 Apr;87(4):281-6. doi: 10.1007/s12098-020-03263-6.

19. World Helath Organization. Emergencies preparedness, response. Pneumonia of unknown origin–China. Disease outbreak news. 2020 Jan 5 [cited 2020 Nov 20]. Available from: https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en.

20. Sabino-Silva R, Jardim AC, Siqueira WL. Coronavirus COVID-19 impacts to dentistry and potential salivary diagnosis. Clin Oral Investig. 2020 Apr;24(4):1619-1621. doi: 10.1007/s00784-020-03248-x.

21. Stoecklin SB, Rolland P, Silue Y, Mailles A, Campese C, Simondon A, et al. First cases of coronavirus disease 2019 (COVID-19) in France: surveillance, investigations and control measures, January 2020. Euro Surveill. 2020 Feb;25(6):2000094. doi: 10.2807/1560-7917.ES.2020.25.6.2000094.

22. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727-733. doi: 10.1056/NEJMoa2001017.

23. Xie X, Li Y, Sun H, Liu L. Exhaled droplets due to talking and coughing. J R Soc Interface. 2009 Dec;6 Suppl 6(Suppl 6):S703-14. doi: 10.1098/rsif.2009.0388.focus.

24. Organization WH. Global Surveillance for human infection with novel coronavirus (2019-nCoV): interim guidance, 31 January 2020 [cited 2020 Nov 20]. Available from: https://apps.who.int/iris/handle/10665/330857.

25. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061-9. doi: 10.1001/jama.2020.1585.

26. Thoracic S. [Expert consensus for bronchoscopy during the epidemic of 2019 novel coronavirus infection (Trial version)]. Zhonghua Jie He He Hu Xi Za Zhi. 2020 Mar 12;43(3):199-202. doi: 10.3760/cma.j.issn.1001-0939.2020.03.012. Chinese.

27. World Helath Organization. Infection prevention and control of epidemic-and pandemic-prone acute respiratory infections in health care. 2014 Apr 7 [cited 2020 Nov 20]. Available from: https://www.who.int/publications/i/item/infection-prevention-and-control-of-epidemic-and-pandemic-prone-acute-respiratory-infections-in-health-care.

28. Otter JA, Yezli S, Salkeld JA, French GL. Evidence that contaminated surfaces contribute to the transmission of hospital pathogens and an overview of strategies to address contaminated surfaces in hospital settings. Am J Infect Control. 2013 May;41(5 Suppl):S6-11. doi: 10.1016/j.ajic.2012.12.004.

29. Baghizadeh Fini, M. Transmission routes of SARS-CoV-2 in dentistry: a literature review. Int J Sci Res Dent Med Sci. 2020;2(4):135-7. doi: 10.30485/ijsrdms.2020.252402.1088.

30. Zuanazzi D, Arts EJ, Jorge PK, Mulyar Y, Gibson R, Xiao Y, et al. Postnatal identification of Zika virus peptides from saliva. J Dent Res. 2017 Sep;96(10):1078-1084. doi: 10.1177/0022034517723325.

31. Barzon L, Pacenti M, Berto A, Sinigaglia A, Franchin E, Lavezzo E, et al. Isolation of infectious Zika virus from saliva and prolonged viral RNA shedding in a traveller returning from the Dominican Republic to Italy, January 2016. Euro Surveill. 2016;21(10):30159. doi: 10.2807/1560-7917.ES.2016.21.10.30159.