Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER 4

Viral Diseases Transmissible by Kissing

Viral infections can be transmitted by various routes. At one extreme, airborne or droplet viral infections (e.g., varicella zoster, ebola) are highly contagious. Most viruses can be spread by touching surfaces contaminated by the virus and then touching the mouth or eyes. Mass gatherings,[1] clinical and chronic care facilities may be hotspots for virus spread when transmission is via aerosols, droplets, or fomites (contaminated surfaces). Environmental factors which are often important for virus survival may include the ambient humidity, temperature, and pH of the environment they are in, so many viruses survive only a few hours in the environment and are often readily inactivated by common hygiene techniques, using soap and water, and some detergents, disinfectants, and antiseptics. Sexually transmitted viral infections, such as herpes simplex, are often transmitted by close mucosal contacts.

Virus infections may be seen especially in immunocompromised people and can be life-changing or even lethal. Some viruses, such as herpes simplex viruses, can also cause obvious oral lesions. Some mainly affect animals but can transmit to man (zoonoses), and viruses may mutate.

4.1 VIRUS IN SALIVA

Various viruses habitually colonize the human mouth and may be present in saliva in quantities sufficient to infect other individuals.[2] Even in instances where ductal saliva might contain no bugs, whole saliva may contain infectious agents from other sites. For example, people who carry respiratory viruses often also have the virus in their saliva[3] as may some who have viral gastroenteritis, and where there is oral bleeding, blood-borne viruses may be present. Humans can be reservoirs of viruses; asymptomatic shedding before clinical disease or where the infection is subclinical (undiagnosed or symptomless) is a major factor in their spread. Host innate or acquired immunity, and saliva can be protective against many infections which may be increased in people

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with immunocompromising states or hyposalivation. Genetic factors play a role in transmission; e.g., the Major Histocompatibilty Complex has a role in *Human Immunodeficiency Virus* (HIV) control, along with virus survival and other factors.

Kissing may spread viral agents from person-to-person if the recipient is susceptible. Kissing often occurs alone while, in sexual interplay, there is usually also kissing, especially deep kissing, and there may be oro-anogenital contact and transmission of viruses.[4]

Viruses responsible for diseases such as hepatitis viruses, herpesvirus infections (e.g., with *Herpes simplex types 1 and 2*, *Epstein-Barr virus*, *Cytomegalovirus*, and *Kaposi syndrome herpesvirus*), and *papilloma-viruses* can be conveyed by kissing—as can potentially other viruses present in saliva such as *Ebola* and *Zika viruses*.

It may be difficult or impossible to differentiate saliva transmission from that by body fluids or fomites introduced into the mouth, respiratory droplets, aerosols, or other routes. Reliable studies are needed, designed specifically to clarify which diseases can be transmitted in humans by saliva in order to develop appropriate strategies to control person-to-person spread of infection by this route.

In an ideal world, the implication of viruses in diseases is best achieved using a modification of Koch's postulates[5] as follows:

1. A nucleic acid sequence belonging to a putative pathogen should be present in most cases of an infectious disease. Microbial nucleic acids should be found preferentially in those organs or gross anatomic sites known to be diseased, and not in those organs that lack pathology.
2. Fewer, or no, copy numbers of pathogen-associated nucleic acid sequences should occur in hosts or tissues without disease.
3. With resolution of disease, the copy number of pathogen-associated nucleic acid sequences should decrease or become undetectable. With clinical relapse, the opposite should occur.
4. When sequence detection predates disease, or sequence copy number correlates with severity of disease or pathology, the sequence−disease association is more likely to be a causal relationship.
5. The nature of the microorganism inferred from the available sequence should be consistent with the known biological characteristics of that group of organisms.
6. Tissue-sequence correlates should be sought at the cellular level: efforts should be made to demonstrate specific *in situ* hybridization of

microbial sequence to areas of tissue pathology and to visible infection or to areas where microorganisms are presumed to be located.
7. These sequence-based forms of evidence for microbial causation should be reproducible.

Such data for viruses in saliva are sparse so in the meantime epidemiological data and the presence of virus in saliva, nucleic acid, or antigens of microorganism have to be relied upon as circumstantial evidence. Most evidence for the presence of viruses in saliva comes from salivary culture, or serological responses, but nucleic acid amplification techniques such as Reverse Transcription Polymerase Chain Reaction (RT-PCR) can now be used and have detected many previously undetectable virus infections.

Some of the implications of viruses in oral healthcare are reviewed elsewhere[2,6] and antiviral activities of saliva have been reviewed elsewhere[7,8] but this is an exploding field[9] so here we review viruses classification (Table 4.1) and the main human viruses detectable in saliva (Table 4.2).

4.1.1 Adenoviruses (HAdV)

At least 69 HAdV genotypes are recognized. HAdV are a common cause mainly of respiratory infections and, typically in men who have sex with men, a cause of urethritis and conjunctivitis.[50] Respiratory infection caused by HAdV in immunocompetent people is typically caused by HAdV-3, mild and self-limited. However, more recently HAdV-55 in particular has been found to cause severe community-acquired pneumonia and acute respiratory distress syndrome in immunocompetent adults,[51] mainly from China. HAdV pneumonia typically is found in neonates, immunocompromised people, and school or military camp populations. HAdV infections in immunocompromised individuals can be severe and life-threatening. The past decade has also seen the emergence in resource-rich countries of several other new viruses—often in traveling people—including HAdV-14p1.[52] HAdV can be found in saliva[3] and it is presumed that it can transmit infection though the main routes are through respiratory droplets or touching infected objects. *Adenoviruses* can survive a long time on objects and spread easily. Adenoviral shedding in saliva and feces has also been reported after p53 adenoviral gene therapy in some patients with esophageal cancer.[53]

Table 4.1 Virus Classification	
Family	**Genus**
DNA Viruses	
Adenoviridae	*Adenovirus*
Papovaviridae	*Papillomavirus*
Parvoviridae	*B19 parvovirus*
Herpesviridae	*Herpes simplex virus, Varicella zoster virus, Cytomegalovirus, Epstein-Barr virus,* HHV-6, HHV-7, HHV-8
Hepadnaviridae	*Hepatitis B virus*
Polyomaviridae	*Polyomavirus* (progressive multifocal leucoencephalopathy)
RNA Viruses	
Bunyaviridae	*Hantaviruses*
Caliciviridae	*Norwalk viruses, Hepatitis E virus*
Coronaviridae	*Coronaviruses*
Flaviviridae	*Dengue virus, Hepatitis C virus, Yellow fever virus, Zika virus*
Filoviridae	*Ebola virus, Marburg virus*
Orthomyxoviridae	*Influenza virus*
Paramyxoviridae	*Measles virus, Mumps virus, Respiratory syncytial virus*
Picornaviridae	*Poliovirus, Rhinoviruses, Hepatitis A virus*
Reoviridae	*Reovirus, Rotavirus*
Retroviridae	HIV-1, HIV-2, HTLV-I
Rhabdoviridae	*Rabies virus*
Togaviridae	*Rubella virus*

Table 4.2 Medical Viruses Detectable in Saliva (Alphabetical Order)		
Virus	**Healthy/Asymptomatic Population (Reference)**	**Active Infection Patients (Reference)**
Adenovirus	NAI	Robinson et al. (2008)[3]
Chikungunya	NAI	Gardner et al. (2015)[10]
Coronavirus-MERS	NAI	Goh et al. (2013)[11]
Coronavirus-SARS	NAI	Wang et al. (2004)[12]
Cytomegalovirus (CMV; HHV-5)	Cannon et al. (2014)[13]	Pinninti et al. (2015)[14]
Dengue virus	NAI	Andries et al. (2015)[15]
Ebola virus (EBOV)	NAI	Bausch et al. (2007)[16]
Enteroviruses	Graves et al. (2003)[17]	NAI
Epstein-Barr virus (EBV; HHV-4)	Ikuta et al. (2000)[18]	Balfour et al. (2013)[19]
Hantavirus	NAI	Pettersson et al. (2008)[20]
Hepatitis A virus	NAI	Joshi et al. (2014)[21]
Hepatitis B virus	NAI	Arora et al. (2012)[22]

(*Continued*)

Table 4.2 (Continued)

Virus	Healthy/Asymptomatic Population (Reference)	Active Infection Patients (Reference)
Hepatitis C virus	NAI	Hermida et al. (2002)[23]
Hepatitis G virus	Yan et al. (2002)[24]	Seemayer et al. (1998)[25]
Herpes simplex virus type 1 (HSV-1; HHV-1)	Miller and Danaher (2008)[26]	Gilbert (2006)[27]
Herpes simplex virus type 2 (HSV-2; HHV-2)	Tateishi et al. (1994)[28]	NAI
Human herpesvirus 6	Zerr et al. (2005)[29]	Leibovitch et al. (2014)[30]
Human herpesvirus 7	Magalhães et al. (2010)[31]	Watanabe et al. (2002)[32]
Human herpesvirus 8 (HHV-8; KSHV)	De Souza et al. (2007)[33]	Vieira et al. (1997)[34]
Human immunodeficiency virus (HIV)	NAI	Navazesh et al. (2010)[35]
Human papillomavirus (HPV)	Kreimer et al. (2010)[36]	Lopez-Villanueva et al. (2011)[37]
Influenza viruses	NAI	Bilder et al. (2011)[38]
Measles virus	NAI	Oliveira et al. (2003)[39]
Metapneumovirus	NAI	NAI
Molluscum contagiosum virus	NAI	NAi
Mumps virus	NAI	Royuela et al. (2011)[40]
Nipah virus	NAI	Luby et al. (2009)[41]
Norovirus	NAI	NAI
Parainfluenza viruses	NAI	NAI
Parvovirus	NAI	NAI
Polyomavirus	Robaina et al. (2013)[42]	Loyo et al. (2010)[43]
Rabies virus	NAI	Crepin et al. (1998)[44]
Respiratory Syncytial Virus (RSV)	NAI	Robinson et al. (2008)[3]
Rhinoviruses	NAI	NAI
Rotaviruses	NAI	NAI
Rubella virus	NAI	Jin et al. (2002)[45]
Torque teno virus	Naganuma et al. (2008)[46]	NAI
Varicella zoster virus (VZV; HHV-3)	Mehta et al. (2004)[47]	Mehta et al. (2008)[48]
West Nile virus	NAI	NAI
Yellow fever virus	NAI	NAI
Zika virus (ZIKV)	NAI	Musso et al. (2015)[49]

NAI, no available information; MERS, Middle East Respiratory Syndrome; SARS, Severe Acute Respiratory Syndrome; KSHV, Kaposi's sarcoma-associated herpesvirus.

4.1.2 Chikungunya Virus (CHIKV)

CHIKV is a *lavivirus* transmitted mainly by *Aedes aegypti* and *Aedes albopictus* mosquitoes, causing fever and joint pains—similar to Dengue fever.

CHIKV can be present in saliva—confirmed by RT-PCR—and especially associated with oral/nasal hemorrhagic lesions in the viremic period.[10] Since more than 50% of CHIKV-infected people experience gingival bleeding,[54] this could also encourage infection transmission by kissing. Nonvector-based mother-to-child transmission of CHIKV has been reported.[55] The impact of potential CHIKV transmission via saliva needs to be more seriously assessed as it could be highly relevant, especially in immunocompromised patients.[56]

4.1.3 Coronaviruses (CoV)

Coronaviruses are common viruses that can infect humans, and animals as diverse as bats and alpacas. There are a number of *Human coronaviruses* and they usually cause respiratory infections—mostly mild illnesses such as the common cold. However, several *coronaviruses* including the Middle East Respiratory Syndrome (MERS), especially seen in Saudi Arabia or visitors to that area, and *Severe Acute Respiratory Syndrome* (SARS), seen mainly in China and travelers from there, can cause more severe and sometimes life-threatening human infections.[52,57] *Coronaviruses* that cause severe acute respiratory infections have $>50\%$ mortality rates in older and immunosuppressed people.[58] WIV1-CoV, a virus similar to SARS, could also be poised to cause epidemics.[59]

People living with or caring for someone with a *coronavirus* infection are most at risk of developing the infection themselves. *Coronavirus* transmission is mainly oral−fecal and respiratory from small droplets of saliva or on fomites. Oral−urine and saliva transmission of MERS-CoV and SARS-CoV are also highly likely.[11,12] Salivary cystatin D, a cysteine protease inhibitor, can inhibit replication of some *coronaviruses*.[60] Although evidence is sparse, SARS-CoV appears to be transmitted primarily through saliva droplets. Kissing could constitute a route for transmission.

4.1.4 Dengue Virus (DENV)

DENV, transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes, is the most important arthropod-borne flavivirus virus affecting

humans and, although most infections are asymptomatic or cause only a mild fever, is capable of producing life-threatening hemorrhagic fever, shock syndrome, and systemic complications (e.g., encephalitis and hepatitis).

DENV has been isolated from human saliva and urine.[15,61–63]

Human salivary transmission of dengue appears to be most unlikely.

4.1.5 Ebola Virus (EBOV)

EBOV is a highly lethal *flavivirus* infection, transmitted via bats and mammalian (monkey and ape) bush meat, causing hemorrhagic fever in humans. EBOV is shed in a wide variety of bodily fluids, including saliva, especially during the acute illness.[16] In a series of eight seriously ill people with Ebola disease, all oral fluid samples obtained 5–10 days after the onset of symptoms were positive for EBOV by RT-PCR.[64] Patients with detectable EBOV in saliva show a higher mortality which likely reflects increased virus shedding in patients with high viremia, an indicator of a poor prognosis.[65]

Human-to-human transmission of EBOV is mainly through direct contact with the tissues, blood, secretions, or other body fluids, including saliva, of infected hosts.[66] Particular concern is the frequent presence of EBOV in saliva early in the course of Ebola disease.[16] Moreover, the person-to-person transmission risk increases—bearing in mind that 1–6% of infected individuals are asymptomatic or mildly symptomatic and the incubation period could last up to 21 days.[66] EBOV could be transmitted to others via saliva by sharing food and through intimate contact, although up to date the only documented cases of secondary transmission from recovered patients have been through sexual transmission.[67] No cases of Ebola transmission through deep kissing have been confirmed, although there must surely be a very high potential risk. In West Africa, the kissing of dead bodies is a traditional burial practice and can promote EBOV transmission.[68]

4.1.6 Enteroviruses (EV)

At least 70 serotypes of EV that can infect humans have been identified, including mainly, *Coxsackieviruses* (*groups A* and *B*), *ECHOviruses*, and *polioviruses*. Recently, the EV genus has been reclassificated in five species: *Human enteroviruses A, B, C*, and *D* and *Poliovirus*. *Enteroviruses a*re implicated in a range of diseases, some of which may affect the

mouth, including herpangina and hand-foot and mouth disease (HFMD) which are common and in which complications including pneumonia, meningitis, or encephalitis are seen but rarely. Animals may be affected by similar conditions (such as foot and mouth disease) but these only rarely transmit to man.[69] *Enteroviruses* have also been detected by PCR in saliva of asymptomatic children.[17]

4.1.6.1 Herpangina

Herpangina is typically caused by *Coxsackieviruses* A1 to 6, 8, 10, and 22. Other cases are caused by *Coxsackie* group B (strains 1–4), ECHOviruses, and other *enteroviruses*. Papulovesicular oropharyngeal lesions progress to ulcers and there is usually no rash.[70]

Children with *Coxsackie* A2 infections mostly present with herpangina only, and have fewer central nervous system complications and a better outcome than those with *Enterovirus* 71 (EV71) infections.[71]

4.1.6.2 Hand, Foot, and Mouth Disease

Hand, Foot, and Mouth Disease (HFMD) is an exanthem on the hands and feet with associated fever and oral lesions.[70] HFMD, is typically a mild illness, caused mainly by Coxsackievirus A16 or EV71,[72] occasionally by *Coxsackieviruses A4–7*, *A9, A10, B1–B3*, or *B5*. Indeed, over 100 serotypes of enterovirus species may cause HFMD.[73]

4.1.6.3 Paraechoviruses (HPeV)

HPeV types 1 and 2, were previously known as *ECHOviruses 22* and *23*, respectively, and can be associated with gastrointestinal, respiratory, or meningeal infections.[74]

4.1.6.4 Poliovirus

Poliomyelitis, which is potentially lethal, is now extremely rare. *Poliovirus* was found in secretions from the upper respiratory tract and salivary swabs of household contacts of patients with virologically proven poliomyelitis.[75]

Enteroviruses are highly contagious, spread mainly by oral–oral and fecal–oral routes, and typically affect children under 10 years old. It has been speculated that respiratory transmission of enteroviruses by droplets from the oral cavity may also explain the high secondary infection rate within households in some outbreaks. It has been suggested that the primary replication sites for enteroviruses could be in the oral cavity and/or gastrointestinal tract, with person-to-person transmission most

commonly occurring via fecal–oral and oral–oral routes.[76] It has also been speculated that *Coxsackie A16* virus is spread through direct contact with the saliva, mucus, or feces of an infected person,[77] but to date there is no evidence supporting transmission by kissing.

In experimental animal models, *Coxsackie B virus* was recovered in the whole saliva of rabbits as early as 2 minutes after injection of virus into an ear vein and it was suggested that virus might be transmitted by saliva of viremic animals without infection of the oropharyngeal tissues.[78]

EV71 is an important public health problem in Asia as it spreads easily to close contacts[79] and may cause central nervous system involvement, serious illness, or death.[80] ECHOvirus 9 strains have been isolated from the saliva of a mother and daughter, both suffering acute salivary gland swelling, but with negative tests for mumps virus.[81]

The evidence suggests that *enteroviruses* could be transmitted through saliva or via kissing.

4.1.7 Hantaviruses

Hantaviruses are zoonoses, rodents being the natural hosts. *Hantaviruses* cause mainly hemorrhagic fever with renal syndrome (HFRS) and *Hantavirus* cardiopulmonary syndrome (HCPS) but there are other forms.

Transmission to humans is usually by inhalation of aerosolized virus-contaminated rodent excreta. *Hantavirus* RNA has also been detected in saliva of patients with HFRS[20] and from *Puumala hantavirus*–infected people.

Human-to-human transmission of *hantaviruses* appears rare, except in the case of *Andes virus* (ANDV).[82] It has been speculated that ANDV may be secreted into saliva, which might be a transmission route for ANDV between humans,[83] but there is no reliable evidence, and there is some evidence of salivary inhibitory factors.[84] *Hantaan hantavirus* appears to be inhibited by salivary mucin—though resistant to histatin 5, lysozyme, lactoferrin, and SLPI.[84]

A prospective study of household contacts of patients with HCPS concluded that transmission risks increased in people partaking in deep

kissing or sex with an infected individual.[85] The evidence suggests that *hantaviruses* could be transmitted through deep kissing.

4.1.8 Hepatitis Viruses

There is a number of hepatotropic viruses, *Hepatitis A, B,* and *C viruses*, and others (e.g., EBV) which can cause hepatitis and may be present in saliva as well as blood and other body fluids, such as semen and gastric juices. Hepatitis A is typically transmitted predominantly by the oro-fecal route and causes a transient illness with hepatitis and no serious sequelae. Hepatitis B and C (formerly hepatitis non-A, non-B) virus infections however are transmitted mainly parenterally—blood transfusion and intravenous drug use being the most frequent risk factors, though sexual transmission may also occur. Illness may be prolonged with chronic carriage and can also cause complications such as cirrhosis and hepatocellular carcinoma.

4.1.8.1 Hepatitis A Virus (HAV)

HAV-RNA may be found in oral fluids[86] though it is present in low frequencies in saliva from HAV-infected patients[21] while others failed to detect it in saliva obtained during a *Hepatitis A virus* outbreak.[87] It seems that saliva can be a potential route of transmission.

4.1.8.2 Hepatitis B Virus (HBV)

HBV-DNA has been detected in saliva from viremic HBV-infected subjects.[88] Transmission has been demonstrated by subcutaneous inoculation of HBV-infected saliva into animals,[89] but the role of saliva in the person-to-person transmission of HBV infection is still not completely defined. Hepatitis B surface antigen (HBsAg) was found in saliva of 76% of patients with severe hepatitis and in 81% of chronic carriers.[90] It has been implied that transmission may be directly from mouth-to-mouth by kissing or by the exchange of saliva on chewed toys and candies[90] but no infections have been confirmed in susceptible persons with an intact oral mucosa who were orally exposed to HBV-infected saliva[91] or students who had oral exposures to HBsAg-positive saliva via contaminated musical instruments.[92] HBV has been transmitted by a human bite,[93] and a case of HBV transmission has been reported in a person who developed hepatitis B presumably after deep kissing with his partner.[94]

However, saliva has a HBV load 1000−10,000 times lower than blood, so the possible transmission of HBV by contaminated saliva

remains low.[89,95–97] There are no reports of HBV transmission during mouth-to-mouth ventilation or cardiopulmonary resuscitation (CPR) training with a mannequim.[98–100]

The evidence therefore points to the possible transmission of HBV via saliva being low.

4.1.8.3 Hepatitis C Virus (HCV)

HCV is transmitted primarily through blood-to-blood contact though 62% of chronic carriers may have HCV-positive saliva.[101–103] HCV-RNA can be detected in the saliva of HCV-infected patients,[23] which might provide an argument for the possible transmission of HCV via saliva, but the salivary HCV viral load is significantly lower than the blood viral load.[104] HCV-RNA in saliva is associated with the level of serum viral load but not with periodontal or liver disease severity.[105] No case of transmission by HCV after mouth-to-mouth ventilation has been described.[106] Transmission of HCV in CPR using CPR mannequins has not been reported even when exposed to HCV-contaminated saliva.[107]

Saliva may therefore be a source of occasional transmission of HCV,[108] particularly where there is deep kissing and there are oral mucosal lesions[109] though epidemiological studies suggest that the infective capacity of HCV in saliva is only low.[110]

4.1.8.4 Other Hepatotropic Viruses

Other hepatotropic viruses, such as *Hepatitis G virus* (HGV), have been found in saliva both from HGV-infected patients[25] and from non-hepatitis patients with oral diseases,[24] but transmission via saliva has not been demonstrated.

4.1.9 Herpesviruses

Human herpesvirus (HHV) infections are common, seen especially in younger people subclinically or producing fever and mucocutaneous lesions, and then remain latent but can be reactivated if immunity wanes. Many can be oncogenic. Oral disease associations examined have ranged from carcinogenesis[111,112] to periodontitis.[113]

4.1.9.1 Herpes Simplex Virus Type 1 (HSV-1; HHV-1)

Congenital HSV infection may result in fetal abnormalities in the TORCH (Toxoplasmosis, Other agents, Rubella, *Cytomegalovirus*, and *Herpes simplex*) syndrome. HSV-1 is typically acquired early in life, usually from direct contact with infected saliva or skin vesicles.[114] HSV can

cause oral lesions mainly as gingivostomatitis, with recurrences usually as herpes labialis. *HSV type 1* DNA can be found in most cases of recurrent herpes labialis, both before and after the appearance of clinical lesions.[27] Furthermore, viral shedding with viral loads sufficient to be transmitted is more frequent than previously thought, even in otherwise healthy HSV-seronegative individuals.[26] HSV ulceration and recurrences and almost certainly shedding are increased and often more extensive in immunocompromised people such as those with HIV/AIDS or post-transplantation and after oral surgical procedures.[115]

HSV can survive up to 88 hours in dry gauze and 1.5 hours on hard surfaces[115] and has the potential to be spread by fomites.[116] From 2% to 10% of adults without clinical signs of disease have HSV-1 in their saliva.[117,118] HSV-1 transmission via saliva is thought to be common and though evidence is sparse it has been transmitted by mouth-to-mouth ventilation.[119–121] However, it is more likely that uninfected adults may contract HSV by kissing[122] or sexual practices but there is little hard evidence to confirm this.

4.1.9.2 Herpes Simplex Virus Type 2 (HSV-2; HHV-2)

HSV-2 typically causes anogenital herpetic lesions and infection is usually transmitted sexually. As with HSV-1, HSV-2 is capable of causing both anogenital and oral disease. Data from a limited number of studies indicate that HSV-2 shedding in saliva is uncommon and symptomless in healthy individuals[28] and usually occurs in the setting of simultaneous anogenital involvement.[123] Men who have sex with men and HIV-positive persons have slightly higher rates of oral HSV-2 shedding than do otherwise healthy individuals.[124,125] However, some studies showed an incidence of HSV-2 in saliva of HIV-infected patients as low as that detected in controls.[126] On the contrary, high HSV-2 salivary detection rates have been reported among Brazilian HIV-infected and healthy children (4.2% and 8.3%, respectively).[127] HSV-2 may not be detected in the saliva of HIV-seropositive persons undergoing highly active antiretroviral therapy.[128] Based on a study on *herpesvirus* prevalence among 16-year-old Swedish girls, it was suggested that "transmission of *herpesviruses* is common in adolescence, and sex, even with regard to its close association with kissing, is one important determinant"[129]; however, in that series antibodies to HSV-2 were seen only in 1% of participants, and to date kissing transmission has not been reliably demonstrated.

4.1.9.3 Varicella Zoster Virus (VZV; HHV-3)

VZV causes mainly varicella (chickenpox) and zoster (shingles) but there can be more serious complications including meningoencephalitis, and occult forms of VZV-induced disease, including zoster sine herpete and enteric zoster. VZV lesions and recurrences are increased and often more extensive in immunocompromised people such as those with HIV/AIDS or posttransplantation.[130] Chickenpox is highly contagious—spread is mainly airborne.[131] VZV-DNA has also been found in the saliva of patients with clinical VZV infections, being detectable before just the varicella rash appears and for 1–2 weeks thereafter.[132] VZV can also be found in saliva in zoster[48] and VZV meningoencephalitis.[133] Saliva samples from individuals aged older than 60 years show VZV in those with a history of zoster, as well as in some healthy older controls with no history of zoster.[134] VZV may also be found in saliva after VZV immunization.[135] Nevertheless, it has been suggested that the detection of VZV-DNA in saliva may be useful in the diagnosis of atypical cases of varicella, zoster sine herpete, neurological syndromes when cerebrospinal fluid is not available and in Bell's palsy, and atypical pain syndromes.[132] It has been suggested that stress favors VZV shedding in saliva, as was shown in a group of asymptomatic astronauts, both during and after space flights.[47] VZV is not detected in saliva from healthy adults.[136] Though there is little reliable evidence of the potential for VZV transmission via saliva, it is highly likely in the scenarios discussed earlier.

4.1.9.4 Epstein–Barr Virus (EBV; HHV-4)

Primary EBV infection in young children is usually subclinical. EBV clinical infection—infectious mononucleosis (glandular fever)—is seen mainly in children older than 10 years, adolescents, and young adults,[137] who present mainly with lymphadenopathy and sore throat.

Patients with infectious mononucleosis can shed EBV in saliva for months.[138] EBV-DNA loads in saliva during convalescence are high and associated with continued infectivity.[139] There is a high prevalence of EBV in saliva and throat washings from healthy children and adults in some geographical regions[18] and by adulthood, at least 90% of all people are seropositive to EBV. EBV may particularly be found in saliva when it is reactivated in immunocompromised people such as those with HIV/AIDS or posttransplantation[140,141] and in oral hairy leukoplakia.[142]

EBV replicates in oropharyngeal epithelial cells and can be spread through saliva.[143] EBV can be transmitted by kissing; prospective epidemiological studies in undergraduate university students have confirmed salivary transmission of EBV[19] though some authors criticized the study methods used.[144] EBV is also called "the Kissing Virus."[145] One anecdote is of a man with infectious mononucleosis who, for 12 hours, had shared a train carriage compartment with a women whom he had not met before and whom he never saw again but during the time in the train, they had repeatedly kissed intimately and some weeks later she developed infectious mononucleosis.[146] A large EBV viral load may be acquired during sexual intercourse[147] and presumably it can also be transmitted from carriers who cough.[144]

Even so, despite the lack of direct evidence, EBV transmission is most likely from saliva, especially by kissing.[19]

4.1.9.5 Cytomegalovirus (CMV; HHV-5)

CMV is another cause of "glandular fever" seen mainly before adulthood, and most adults have been previously infected with CMV but the virus may be reactivated in patients with immunocompromising conditions, e.g., HIV infection[148] and posttransplantation.[149] Multiple CMV strains are recognized and, in men who have sex with men coinfected with HIV, infections with several strains may be seen.[150] Infection by CMV B groups,[151] particularly CMV glycoprotein gB1 subtype (gB1) appear to cause most morbidity.[151,152]

CMV is also one of the most important known viral causes of fetal abnormalities (TORCH syndrome). CMV shedding in body fluids is seen in TORCH and also increased where there is reactivation in immunocompromised people.[141] CMV-seropositive children, especially infants, may be a high infective risk to pregnant women, mainly via saliva. Transmission is common in day care centers.[153]

Real-time PCR of saliva is the gold-standard diagnostic test for detection of CMV.[14] As well as CMV shedding in body fluids in immunocompromised people, apparently healthy but CMV-seropositive children can also shed CMV at high levels in saliva for months, highlighting the potentially high transmission risks posed by saliva,[13] probably the principal postnatal transmission route.[154]

Although there is no robust evidence of a risk of CMV transmission associated with kissing, this is a highly probable route.[155]

4.1.9.6 Human Herpesvirus 6 (HHV-6)

HHV-6 can cause a range of diseases from exanthema subitum (roseola infantum), mononucleosis syndromes, and pneumonitis to encephalitis.[156] Following primary infection, viral genomes may persist in peripheral blood and saliva of most apparently healthy individuals.[30,157] Serological studies indicate that HHV-6 infects most children by age 2 years and that older siblings serve as a source of transmission.[29] HHV-6 has a number of forms—HHV-6, HHV-6B, and also CiHHV-6, which is chromosomally integrated[158,159] and can be reactivated.

HHV-6 may be present in saliva from healthy adults[31] but even immunosuppression by AIDS has little effect on HHV-6 shedding in saliva.[160]

HHV-6 transmission may occur via an oral route.[161]

4.1.9.7 Human Herpesvirus 7 (HHV-7)

HHV-7 infection is usually a benign and self-limited disease of childhood and rarely has complications though it may affect the central nervous system. It has been implicated in pityriasis rosea and, like HHV-6 it can also cause exanthem subitum.

HHV-7 DNA has been detected in saliva from practically all patients with pityriasis rosea[32] and frequently from healthy adults, particularly women, with regional variations.[31,162–164] HHV-7 is present in saliva in adults, and immunosuppression increases both frequency of detection and viral load.[160]

HHV-7 may well be transmitted person-to-person via saliva.[165]

4.1.9.8 Human Herpesvirus 8 (HHV-8; Kaposi Sarcoma Herpesvirus; KSHV)

HHV-8 (KSHV) can cause Kaposi's sarcoma (KS), primary effusion lymphoma, and multicentric Castleman's disease. KSHV infection is endemic in sub-Saharan Africa, the Mediterranean littoral, and China (Xinjiang region), but Western Europe and United States have a low prevalence. KSHV is found mainly in immunocompromised people such as those with HIV/AIDS or posttransplantation.

KSHV is detectable in more than 90% of KS lesions,[166,167] and oral replication is an essential feature of infection.[168]

In areas of high HIV prevalence, such as sub-Saharan Africa, the Mediterranean littoral, and the Xinjiang region in China, KSHV can be transmitted sexually or by contaminated blood transfusions and tissue transplants,[169] or via saliva contact.[170] KSHV is found in saliva from some 35%–80% of apparently healthy adults especially from certain geographical regions such as Brazil[33] and also particularly from immunocompromised people.[171] There is a high prevalence of KSHV in the saliva of patients with KS, even in the absence of intraoral lesions.[34]

There is consensus that saliva is the main route of KSHV transmission, especially in children in endemic areas,[172] that household exposure increases the risk for early childhood infection, and that specific feeding behaviors probably play a role in some cases.[173] Occupational transmission of KSHV to healthcare workers is uncommon.[174] However, epidemiological evidence points to particular sexual behaviors, including deep kissing, as being significant transmission risk factors for KSHV after childhood.[175]

4.1.10 Human Immunodeficiency Viruses (HIV)

Human Immunodeficiency Viruses cause HIV disease and the Acquired Immune Deficiency Syndrome (AIDS). The possibility of interpersonal HIV contagion by saliva is often still a common belief[176] and, e.g., some parents fear transmitting HIV to, or catching infection from their children through saliva.[177] However, some 3 decades ago, it was stated that there is no epidemiological evidence that HIV is transmitted by saliva,[178] and, although such transmission is theoretically possible[179] little has changed subsequently.

HIV can indeed be isolated from saliva, but infrequently.[180] Saliva may of course, also contain blood[181] and it has been suggested that HIV may be transmitted after deep kissing,[182] especially if there is blood in the mouth.[183] Hemoglobin concentrations in saliva are higher in HIV-positive intravenous drug abusers (IVDA) than in HIV-negative IVDA and controls, and in AIDS a mean of 1.3 μL blood/mL saliva has been estimated.[183] However, there is only a low level of HIV in saliva even when it is likely contaminated with blood.[184] Transmission to household nonsexual contacts is improbable.[185]

HIV transmission is unlikely with normal household contacts[186] and, although it has been stated by the Centers for Disease Control and Prevention (CDC) that deep kissing might result in viral transmission,[187] CDC now declares that HIV is not spread via saliva, considers open-mouth kissing a low risk for HIV transmission and yet recommends against engaging in this activity with known HIV-infected persons.[188] Nevertheless, CDC has apparently investigated only a single case attributed to contact with blood in the mouth.[189]

Mouth-to-mouth ventilation is not implicated in the transmission of HIV, even though contaminated saliva contacts open wounds.[190] Blood is visible in saliva or vomit in some resuscitations and this with oral microlesions in 50% of healthy rescuers, makes blood-to-blood contact possible.[109]

Nevertheless, even after exposure of healthcare workers to blood-contaminated saliva or blood through accidental needle stick injuries, the risk of infection has been consistently less than 1% and transmission in normal dental practice is improbable.[191]

4.1.11 Human Papillomaviruses (HPV)

HPV can cause benign warty lesions on oral and other epithelia, and some oncogenic types are implicated in cervical, anogenital, and oropharyngeal cancers. A number of viruses have been examined for possible roles in oral carcinogenesis.[112,192–194] including HPV.[195]

A small but noteworthy proportion of clinically healthy individuals have oral HPV infections,[36,196,197] including with HPV types known to cause cancer in the oral region.[198]

One HPV reservoir may be in the gingivae.[199] HPV are often latent, lesions may be small or symptomless and often undetected, and virus may be reactivated by immunoincompetence.[200–204] HPV lesions are often more extensive in immunocompromised people such as those with HIV/AIDS or posttransplantation.[205]

Some years ago, it was suggested that oral cancer might be a sexually transmitted viral infection.[206,207] Early focus on *herpes simplex* virus, turned to HPV. Oropharyngeal cancer in particular has proved to be significantly associated with oral HPV type 16 (an oncogenic HPV) and associated with a high lifetime number of vaginal-sex

partners and oral-sex partners with oncogenic HPV-16 DNA being detected in many (72%) of cancers.[208] HPV-DNA in oral cancer biopsy specimens is more frequent among subjects who reported >1 sexual partner or who practiced oral sex.[209] Oropharyngeal cancer, tonsillar in particular, is increased in patients with anogenital cancer[210] and in females with cervical cancer and in their partners.[211] There have been significant increases in tonsil and base of tongue cancers in males, and base of tongue cancer in females with HPV-associated oropharyngeal cancer are increasing.[212]

HPV horizontal, nonsexual transmission may be responsible for oral infection in children.[213] Household transmission may occur via saliva and the shared use of contaminated objects.[37] Partners may carry the same oral HPV, and persistent oral HPV infection of the spouse increases the risk of persistent oral HPV infection 10-fold in the other spouse.[214] HPV is particularly common in those with oropharyngeal cancer,[215] though in one study partners of patients with HPV-OPC did not seem to have more oral HPV infection compared with the general population.[216]

Sexual behavior may impact on the risk of infection and though some authors consider kissing to be a low-risk activity,[214,217] deep (French) kissing has been associated with the development of oral HPV infection;[218] this finding has been confirmed in epidemiological studies on young adults of both genders[219] and men who have sex with men,[220] but not, in a study based on a questionnaire on sexual behavior of Australian university students, where no significant differences were found in the number of partners for deep kissing, between those with oral HPV infection and HPV-negative students.[221]

In summary, some studies imply therefore that oral HPV may be transmitted by deep kissing or by oral sex (mouth-to-genital or mouth-to-anus contacts), while others have not. The likelihood of contracting HPV from kissing or having oral sex with a person who carries HPV is not therefore, completely certain.[222]

4.1.12 Human Polyomaviruses

Humans may contract infections with *BK polyomavirus* (BKV), *JC polyomavirus* (JCV), or *Merkel cell polyomavirus* (MCV). *Polyomavirus* primary infections generally occur early in life and are implicated respectively in nephropathy, progressive multifocal leukoencephalopathy, and

Merkel cell carcinoma. The role of novel *Human polyomaviruses*, *KI* (KIV), and *WU (*WUV*)* is unclear.

Polyomavirus detection is generally highest among people 15–19 years of age; WUV infections being more frequent between those ages and decreasing later, but BKV excretion peaking and persisting during the third decade of life, and KIV is more common in subjects ≥50 years of age.[42] BKV, JCV, WUV, and KIV are found in the saliva of some healthy individuals[223] and may be transmitted by saliva.[42] *Polyomavirus* reactivation is more common in immunocompromised people and these viruses may be found in saliva from HIV-positive children[224] and in renal transplant recipients.[225]

MCV is widespread in the human body, and in saliva it is more common than in samples from the lung and genitourinary system, so transmission via saliva would seem possible,[43] and MCV may be acquired through close contact between young siblings and between mothers and their children.[226]

BKV has also been detected in saliva from apparently healthy individuals,[42] and salivary gland cells may be a site of virus replication,[227] supporting the hypothesis that saliva may be a route for BKV transmission. In contrast, JCV shedding in saliva is rare.[228]

Thus although saliva may be a route of transmission for some human *polyomaviruses*, the possibility that kissing is a significant risk activity remains to be clarified.

4.1.13 Influenza Viruses

There are three main types of *Human influenza viruses*, *types A* (IVA), *B*, and *C*. All cause severe lower respiratory disease. Nasopharyngeal colonization by *Streptococcus pneumoniae* (*pneumococcus*) is thought to be a prerequisite for developing influenza, and in some older people with influenza-like-illnesses *pneumococci* are plentiful in saliva.[229] Significant decreases in numbers of salivary anaerobic bacterial (CFUs), and neuraminidase and trypsin-like proteases levels after professional oral healthcare suggests that oral hygiene maintenance can be effective in reducing influenza.[230]

H1N1 (swine flu) and some other novel strains of *Influenza viruses* are carried by pigs, poultry, or other birds and several novel viruses

have appeared in resource-rich countries mainly in traveling people.[52] *Avian influenza A (H5N1)* and *A (H7N9) viruses* which circulate widely in some poultry populations and sporadically infect humans include: in eastern China the *H7N9 influenza A virus*, and in the United States a *Swine-like influenza H3N2 variant virus*. Sporadic human cases of avian *A (H5N6), A (H10N8)*, and *A (H6N1)* have also emerged.[231]

Saliva in people with influenza may well contain the virus. About half of the patients with influenza have positive saliva and nasopharyngeal swabs within 24 hours from the onset of symptoms.[232] Saliva sampling for H1N1 is accurate, reliable, and more convenient than a nasopharyngeal swab.[38]

It seems that saliva represents an important initial barrier to *Influenza virus* infection. Consequently, it is unlikely that kissing could constitute a route for transmission.

4.1.14 Measles Virus

The *Measles virus* causes measles, a highly contagious disorder, usually in children manifesting with fever and rash sometimes with more serious complications.[233] Outbreaks of measles communities such as in Gypsy-Travelers are well recognized.[234]

Measles virus is found in saliva,[45,235] where nucleic acid can be amplified by PCR[39] and directly from using a point-of-care test.[236] Measles is usually spread by droplets but kissing may well also transmit the virus.

4.1.15 Metapneumovirus (hMPV)

Human metapneumovirus (hMPV) is a respiratory pathogen that can cause features ranging from asymptomatic infection to severe bronchitis, mainly but by no means exclusively in children, and is therefore clinically similar to infections with *Respiratory syncytial virus, Parainfluenza virus type 1*, and *Human parainfluenza virus type 3.*

hMPV is found in saliva, more in children within 3 days of onset of symptoms than later.[3,237]

Although we found no reliable evidence of the virus transmission by saliva, it is highly likely.

4.1.16 Molluscum Contagiosum Virus

Molluscum contagiosum is a benign *poxvirus* infection of the skin or very occasionally the mucosae. Lesions are seen mainly in children, sexually active adults, and those who are immunocompromised.

We found no reliable evidence of *Molluscum contagiosum virus* in, or transmission by, saliva.

4.1.17 Mumps Virus

Mumps virus typically causes acute sialadenitis (usually parotitis) but is a systemic infection with a variety of possible extra-salivary complications.[238]

Mumps transmission has occurred despite prompt isolation of cases after the onset of parotitis, indicating viral shedding before the onset of parotitis.[239] Mumps transmission can occur from persons with subclinical or clinical infections and during the prodromal or symptomatic phases of illness and within the subsequent 5 days.[240] The CDC, American Academy of Pediatrics (AAP), and Healthcare Infection Control Practices Advisory Committee (HICPAC) recommend a 5-day period after the onset of parotitis, both for isolation of persons with mumps in either community or healthcare settings and for use of standard infection control precautions and droplet precautions.[240]

Mumps virus is transmitted mainly by respiratory droplets but virus can also be found in saliva.[45] *Mumps virus* can be isolated from saliva and throat swabs from 7 days before to 8 days after the onset of parotitis, isolation rates are much greater closer to parotitis onset, the viral load decreasing substantially over the first 4 days after illness onset and becoming extremely low thereafter. The raised salivary load of mumps virus suggests a risk for transmission.[241]

Although we found no reliable evidence of mumps virus transmission by saliva, it is highly likely.

4.1.18 Nipah Virus

Nipah virus (NiV) is a *paramyxovirus*, whose main reservoir host is the fruit bat, first identified in Malaysia and Singapore during an outbreak of encephalitis and respiratory illness in farmers and people with close pig contacts. It is potentially lethal. Though uncommon, person-to-

person transmission of NiV may occur mainly via respiratory secretions and body fluids, including saliva.[41,242–244]

Although we found no reliable evidence of NiV transmission by saliva, it is highly likely.

4.1.19 Noroviruses

Noroviruses (NoV or human Nov (HuNov)) are *calciviruses* which commonly cause acute gastroenteritis (Winter vomiting disease). NoV genogroup I (GI) (includes *Desert Shield virus, Norwalk virus*, and *Southampton virus*) or genogroup II (GII) (includes *Bristol virus, Hawaii virus, Lordsdale virus, Mexico virus, Snow Mountain virus* and *Toronto virus*) causes most infections.[245] Deaths are usually in the very young, old, or immunosuppressed and are rare in resource-rich communities.[246]

Differences in NoV susceptibility relate to factors including histo-blood group antigens (HBGAs) (i.e., the ABO blood group, the Lewis phenotype, and the secretor status), FUT2 (FUcosylTransferase 2), and FUT3 genotypes.[247,248]

Noroviruses are extremely contagious,[249] epidemics being seen mainly in closed communities such as cruise ships and long-stay facilities, and some research suggests as few as five virus particles are enough to transmit infection.[250] NoV can survive for long periods outside a host depending on the surface and temperature conditions. One study found NoV on surfaces used for food preparation 7 days after contamination.[251] It can also survive for months in contaminated water, weeks on hard surfaces, and up to 12 days on fabrics.[252]

There can be feco-oral transmission of NoV but salivary transmission appears poorly documented. It has been suggested that it is impossible to get infected by kissing someone who is not yet showing symptoms. However, it may be possible to catch it from someone who has recently vomited by kissing them, as viral particles may be in their mouth from vomitus.[253]

4.1.20 Parainfluenza Viruses (HPIVs)

Human parainfluenza viruses (HPIVs) are RNA viruses in a group of four distinct serotypes, which commonly cause respiratory illnesses in infants and young children but anyone can suffer HPIV illness of fever,

runny nose, and cough. Furthermore, HPIVs can also cause more severe illness, such as croup or pneumonia.

Most children have been infected by HPIV-3 by age 2 years and by HPIV-1 and 2 by age 5, and HPIVs are found in saliva.[3]

Transmission is mainly respiratory but probably also by saliva.

4.1.21 Parvoviruses

Parvovirus B19 infection may cause erythema infectiosum—a mild fever and rash with oral erythema, and sometimes arthralgia or arthritis. However, severe outcomes of *Parvovirus B19* infection may occur. During pregnancy, *Parvovirus B19* infection of the fetus can cause fetal loss in the first trimester, or extensive hemolysis. In patients with hemolytic anemias, *Parvovirus B19* can produce a transient aplastic crisis. In infants, or in immunocompromised patients, *Parvovirus B19* can cause serious hemolysis.

Parvovirus transmission is mainly via respiratory droplets[254] but could be through saliva.

4.1.22 Rabies Virus

Rabies virus expands worldwide, especially in Asia and Africa. *Rabies virus* can be detected in saliva of rabies patients[255] now with RT-PCR.[44]

Rabies virus is present in fluids and tissues during the first 5 weeks of transmission, but there are few well-documented reports of human-to-human transmission—and these invariably are in corneal[256] or organ transplant recipients.[257]

Although the infection has never been well-documented, human-to-human transmission of rabies following saliva exposure remains at least a theoretical possibility.

4.1.23 Respiratory Syncytial Virus (RSV)

RSV is a common cause of respiratory illness indistinguishable from the common cold, and seen mainly in young children. It may lead to lower respiratory disease. Secretion of blood group antigens is associated with respiratory virus diseases.[258]

RSV can be found in saliva[3,237] and can remain viable for at least 30 minutes on hands or for up to 5 hours on surfaces.

Although we found no reliable evidence of RSV transmission by saliva, it is highly likely.

4.1.24 Rhinoviruses

Rhinoviruses are a frequent cause of the common cold.[259] Transmission is mainly via droplets, but viruses may persist in moist secretions on fomites.

Communicability of *rhinoviruses* showed transmission between partners of 41% and 33% for types 16 and 55, respectively,[260,261] but transmission was rare unless the donor spent hours with the partner and had virus on their hands and anterior nares.

Saliva in adults contains neutralizing antibodies to *rhinoviruses*.[262] Few *rhinovirus* particles survive in saliva and therefore, though transmission via saliva must be possible, normal kissing is not the usual mode of infection spread.

4.1.25 Rotaviruses

Rotaviruses are (with *noroviruses*) the most important causes of acute gastroenteritis, mainly in children. *Rotaviruse*s are highly contagious.

The host secretor status (FUT2 genotype) affects the expression of HBGAs which act as sites for viral attachment to the gastrointestinal, respiratory, and genitourinary tract epithelia.[263] *Rotavirus* VP4 spike protein (VP8*) engages sialic acid in the viral binding to cellular receptors, facilitating viral attachment and entry.[264] In newborns and infants immunized against *rotavirus*, serum and saliva IgA antibodies conceivably assist in protection.[265]

Rotaviruses can be found in saliva and other body fluids in infected patients,[266] presumably transmitting infection.

4.1.26 Rubella Virus

Rubella virus causes infection mainly in children who may be symptomless or develop a rash, fever, and occasionally other symptoms or signs including lymphadenopathy and palatal purpura. Congenital rubella infection may result in TORCH syndrome.

In rubella, the virus RNA can be found in saliva.[45,267] Although we found no reliable evidence of rubella transmission by saliva, it is highly likely.

4.1.27 Torque Teno Viruses (TTV)

TTV was first identified in a patient with non-A-E hepatitis but the viruses are now known to be ubiquitous,[268] with >90% of adults worldwide infected. It has been suggested that TTV infection is associated with many diseases, including some oral disease,[24] with little evidence.

TTV may be detected in saliva.[46] TTV transmission by saliva, though highly likely appears unsupported by reliable evidence.

4.1.28 Yellow Fever Virus

Yellow Fever virus is, like Dengue and Zika, a *flavivirus* transmitted by mosquitoes, usually *A. aegypti*, and is endemic to tropical regions of Africa and the Americas, causing potentially lethal hemorrhagic fever.[269] In Africa, yellow fever occurs in 34 countries and an epidemic in Angola in 2016 caused serious concern and was spread by travelers to at least China, Democratic Republic of Congo, Kenya, and Morocco. At least half of severely affected patients who do not receive treatment die within 14 days.

No human–human transmission of *Yellow* fever virus by saliva has been reported, and we found no reliable evidence of salivary transmission.

4.1.29 West Nile Virus (WNV)

WNV, a *flavivirus*, naturally maintained in a cycle between birds and mosquitoes, with occasional spillover by mosquito bites to humans, since isolated first in Uganda, has spread widely including the United States and Europe.[270] As with so many viruses, most WNV infections are asymptomatic, but there is a risk of potentially lethal neurological disease.

Although a case of possible sexual transmission of WNV has been reported,[271] we found no reliable evidence of WNV transmission by saliva.

4.1.30 Zika Virus (ZIKV)

ZIKV infection is a mosquito-borne, *flavivirus* disease associated mainly with Guillain-Barre syndrome and fetal microcephaly.[272] The magnitude of the current ZIKV epidemic has led to a declaration of a Public Health Emergency of International Concern by the WHO.[273]

ZIKV RNA has been detected in saliva from patients with Zika fever.[49] It has been suggested that the rate of ZIKV detection in saliva samples is higher even than in blood or urine.[49] Saliva and urine samples present higher viral load than serum.[49,274,275] Viral RNA is prolonged shedding in saliva for some weeks after symptom onset—with a slightly longer persistence time than in urine,[274,276] as it has previously been demonstrated for other vector-borne *flaviviruses*. In consequence, saliva has been recommended to test for ZIKV when drawing blood or processing of blood samples may be difficult.[275,276]

Nonvector-borne ZIKV transmission plays a role in the spread of ZIKV.[277] One American scientist contracted Zika while working in Senegal in 2008, and transmitted ZIKV infection to his wife; a sexual transmission of the virus was suggested, but other possibilities such as exchange of other bodily fluids including saliva could not be ruled out; moreover, aphthous-type oral ulcers were observed in both spouses.[278] Here as yet no reliable evidence to support ZIKV transmission through human saliva,[9,279,280] but cytopathic effects have been reported when bringing saliva in contact with Vero cells, which suggests infectious potential.[277]

In a case report of ZIKV infection in a 24-year-old woman who was living in Paris and reported sexual contact with a man who had recently returned from Brazil, the authors could not rule out the possibility that transmission occurred through saliva exchanged through deep kissing,[281] but up to date we found here no reliable evidence of Zika transmission by kissing.

4.2 CLOSING REMARKS AND PERSPECTIVES

The transfer of body fluids might transmit viral infections, many of which are seen especially in immunocompromised people and some can be life-changing or even lethal, as it has happened in a number of catastrophes where viral agents such as *Human Immunodeficiency Viruses* and *hepatitis viruses* were transmitted by blood. Any risks of transmission from saliva appear not well-defined, and reliable evidence for virus transmission through kissing is sparse. Nevertheless, this route may be one where the *flaviviruses* at least may well spread. In this regard, the number of emerging viral diseases has increased dramatically in recent decades. In an ever more global society, the arrival of immigrants requires us to maximise universal barrier measures, in

particular to avoid the transmission of pathogenic viruses not recognised by our immune system. Detection of some of these viruses in saliva, such as *Ebola virus* or *Zika virus* represent a new challenge for prevention of human to human transmission. Efforts are being made regarding the development of strategies for virus detection _including polymerase chain reaction-based methods, paper-based synthetic gene networks, immunoassays, magnetic nanoparticles-based assays or liposome-based detection assays. However, there is still a need to search for and improve upon more sensitive and specific detection methods for these challenging viruses. Substantial numbers oral viruses are shared amongst genetically unrelated, cohabitating individuals; most of these viruses are bacteriophages and their distribution over time within households indicates that they are frequently transmitted between the microbiomes of household contacts.

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