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# Bacterial and viral pathogens in saliva: disease relationship and infectious risk

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Research on the infectious aspects of dental diseases has focused on the internal development and the pathogenicity of dental biofilms, and comparably little attention has been given to the source of the biofilm microorganisms. Odontopathic bacteria exist in saliva before colonizing dental surfaces, and a better understanding of the acquisition of salivary pathogens may lead to new approaches for managing dental diseases. Human viruses are also frequent inhabitants of the human mouth, and their presence in saliva may be caused by the direct transfer of saliva from infected individuals, a bloodborne infection of the salivary glands, infection of the oral mucosa, or serumal exudates from diseased periodontal sites.

It has long been recognized that saliva can contain potential pathogens in quantities sufficient to infect other individuals (152). The classic example of a serious infection contracted through saliva is Epstein–Barr virus-induced mononucleosis, which colloquially is termed the 'kissing disease'. An example from the past is the 'No Spitting' signs to prevent inhalation of the tubercle bacillus from spit specimens on street pavements and public floors. Dental clinics implement stringent infection-control measures to protect personnel and patients from pathogens in spatter, mists, aerosols, particulate matter or contaminated instruments (36) and, in the future, may adopt fully automated test systems to identify saliva-borne pathogens of oral and medical diseases (72, 144).

The potential of salivary biomolecules to aid in the diagnosis of various conditions / diseases is a topic of current interest (209). Highly sensitive and specific molecular detection methods have greatly facilitated the search for salivary molecules of diagnostic value. Polymerase chain reaction (PCR)-based assays can detect a large array of pathogens in saliva with no interference from PCR inhibitors (139), and even more efficient identification techniques are rapidly emerging (97, 132). A major advantage of salivary testing is the ease by which diagnostic samples can be collected by health professionals, by the individuals themselves, or by parents for young children. Salivary sampling is painless and involves fewer health and safety issues than venepuncture, especially in patients with hemorrhagic diseases or virulent bloodborne pathogens. Used as diagnostic aids, salivary biomolecules can identify a variety of cancers, illicit and prescription drug use, hereditary disorders and hormonal irregularities (87). Salivary testing can also screen for infection with the human immunodeficiency virus (HIV) (206), herpesviruses (144, 172), hepatitis viruses (144), measles virus (70) and other pathogenic viruses and bacteria (discussed later). Some biomarkers in saliva exhibit significant intrasubject fluctuations and may have limited diagnostic utility (189).

Salivary microbial assays to assess the presence or the risk of dental diseases are premised on the idea that (i) whole saliva is the immediate source of oral biofilm bacteria, and saliva and dental biofilms tend to harbor similar relative levels of odontopathogens, and (ii) high salivary counts of odontopathic bacteria infer a high risk for dental disease and for pathogen transmission between individuals, and a decrease in the salivary count of pathogens can serve as an indicator of therapeutic effectiveness. Periodontal disease severity may be ascertained by the salivary level of periodontal pathogens or host-response markers (67, 130, 146, 193, 214), and the periodontopathic bacteria may be acquired from the infectious saliva of close family members (17). Caries risk

is assessed by the levels of mutans streptococci and lactobacilli in stimulated saliva (94, 96), and salivary transmission of cariogenic bacteria frequently occurs from the mother to her child (92, 100). Yeasts can be part of oral biofilms and cause candidosis and other oral diseases (157, 210), especially in HIV-infected individuals, and *Candida albicans* transmission between spouses can take place through saliva (26). Comparatively few parasites colonize the mouth, but systemic parasitic infections can affect the oral cavity (e.g. leishmaniasis), and oral protozoa may be more common than once thought (21).

This review article presents evidence that pathogenic bacteria and viruses can be present in saliva at levels that pose a disease risk for individuals with whom saliva is exchanged. Emphasis is placed on the salivary route of transmission of periodontopathic bacteria and herpesviruses, and on the relationship between these infectious agents and periodontitis. The salivary presence of viral pathogens of rare, but serious, medical diseases is also reviewed.

## Bacteria in saliva

Periodontitis and dental caries are infectious diseases, but the exact causes and their relative importance is still a matter of research. The search for etiological factors is closely connected to the question of how to avoid dental diseases. The consensus viewpoint of the scientific community is that specific bacteria cause both periodontitis and dental caries. This understanding has prompted the pursuit of microbiological methods to diagnose, prevent and treat dental infections.

### Periodontopathic bacteria

The periodontopathic microbiota has been studied for the purpose of developing more effective diagnostic tests and treatments (12, 165). As periodontopathic bacteria also colonize the tongue dorsum and other nondental sites (43, 131), and can be transferred via saliva to close family members (17), periodontitis therapeutic measures ought to target periodontal pathogens in the whole mouth, not only in dental biofilms, and may even include entire family units in order to prevent cross-infection.

Umeda et al. (193) compared the presence of six species of periodontopathic bacteria in whole saliva and subgingival plaque from 202 subjects. Each study subject contributed a whole saliva sample and a paper point sample pooled from the deepest periodontal pocket in each quadrant of the dentition, and the test bacteria were identified using a 16S ribosomal RNA-based PCR assay (15). A statistical relationship was found between the presence of *Porphyromonas gingivalis*, *Prevotella intermedia*, *Prevotella nigrescens* and *Treponema denticola* in whole saliva and in periodontal pocket samples, and in the event of disagreement, the organisms were more frequently present in whole saliva than in periodontal pockets ($P < 0.01$). The oral presence of *Aggregatibacter actinomycetemcomitans* and *Tannerella forsythia* was not reliably detected by sampling either whole saliva or periodontal pockets. Other studies also found that a salivary sample alone did not identify all individuals infected with *A. actinomycetemcomitans* (176, 200). Taken together, a sample of whole saliva seems to be superior to a pooled periodontal pocket sample for detecting oral *P. gingivalis*, *P. intermedia*, *P. nigrescens* and *T. denticola*, but samples of both whole saliva and periodontal pockets may be needed in order to detect oral *A. actinomycetemcomitans* and *T. forsythia* with reasonably good accuracy. The reason for this is that *A. actinomycetemcomitans* and *T. forsythia* can persist in nondental sites, as best demonstrated in fully edentulous individuals (55, 194).

Umeda et al. (192) also investigated risk factors for harboring *A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythia*, *P. intermedia*, *P. nigrescens* and *T. denticola* in periodontal pockets, in whole saliva, or in both sites (i.e. orally). The study subjects included 49 African–Americans, 48 Asian–Americans, 50 Hispanics and 52 Caucasians living in Los Angeles. Periodontal probing depth was positively associated with all six study bacteria. African–Americans were at increased risk (compared with Caucasians) for harboring *P. gingivalis* in saliva [odds ratio (OR) 2.95] and orally (OR 2.66), and at reduced risk for harboring *T. denticola* orally (OR 0.34). Asian–Americans showed an increased risk for harboring *A. actinomycetemcomitans* in periodontal pockets (OR 6.63) and for harboring *P. gingivalis* in periodontal pockets (OR 5.39), in saliva (OR 5.74) and orally (OR 5.81). Hispanics demonstrated an increased risk for harboring *A. actinomycetemcomitans* in periodontal pockets (OR 12.27), and for harboring *P. gingivalis* in periodontal pockets (OR 6.07), in saliva (OR 8.72) and orally (OR 7.98). Age was positively associated with the prevalence of *A. actinomycetemcomitans* orally (OR 1.18), and with *P. gingivalis* in saliva (OR 1.20) and orally (OR 1.20). The male gender was a risk factor for harboring *P. intermedia* in periodontal pockets (OR 2.40), in saliva (OR 3.31) and orally (OR

4.25), and for harboring *P. nigrescens* in saliva (OR 2.85). The longer the subjects had resided in the USA, the greater the decrease in detection of *A. actinomycetemcomitans* orally (OR 0.82). Former smokers demonstrated a decreased risk for harboring *A. actinomycetemcomitans* in saliva (OR 0.23), and current smokers displayed an increased risk for harboring *T. denticola* in periodontal pockets (OR 4.61). Current and passive smokers revealed less salivary *P. nigrescens* than nonsmokers (127). In sum, the study found a relationship between the presence of periodontopathic bacteria in whole saliva and in periodontal pockets, and pointed to the importance of genetic or environmental factors in the colonization of these pathogens. Salivary tests for periodontitis may show increased accuracy if supplementing infectious disease variables with ethnic and social factors and with smoking habits (177).

Studies have evaluated the salivary route of transmission of periodontopathic bacteria. Transmission of periodontal pathogens from person to person depends on the salivary load of pathogens in the donor subject and various ecological factors in the recipient (16). An early epidemiologic study found that members of the same family were infected with *A. actinomycetemcomitans* strains of the same biotype and serotype (213). However, even in families with individuals heavily infected with *A. actinomycetemcomitans*, some family members did not harbor the organism, attesting to a relatively poor transmissibility of *A. actinomycetemcomitans* (213). A study based on bacterial typing by means of the arbitrarily primed PCR method revealed an interspousal transmission of *A. actinomycetemcomitans* in 4/11 (36%) of married couples and of *P. gingivalis* in 2/10 (20%) of married couples (17). Parent-to-child transmission of *A. actinomycetemcomitans* took place in 6/19 (32%) families, whereas *P. gingivalis* was not transmitted from parent to child in any of the families studied (17). Similarities in the profile of periodontal bacteria have also been shown for 6- to 36-month-old children and their caregivers (186). A review article described horizontal transmission between spouses to be 14–60% for *A. actinomycetemcomitans* and 30–75% for *P. gingivalis*, and vertical transmission to be 30–60% for *A. actinomycetemcomitans* and to occur only rarely for *P. gingivalis* (197). The intrafamilial transmission of *A. actinomycetemcomitans* and *P. gingivalis* may in part explain the familial pattern of some types of periodontitis (13). Also, periodontal treatment and marked suppression of periodontopathic bacteria in members of a periodontitis-prone family may diminish the risk of transferring the pathogens and the disease to uninfected family members.

## Cariogenic bacteria

The major cariogenic bacteria are mutans streptococci in incipient dental caries and lactobacilli in advanced caries lesions (95), perhaps in combination with other bacteria of the dental biofilm (1, 142). After adjusting for age and ethnicity, 6- to 36-month-old children with high levels of *Streptococcus mutans* were found to be five times more likely to have dental caries than children with low levels of the bacterium (117). Recent large-scale microbiological studies have linked *S. mutans* to crown caries in children and adolescents (1, 42) and to root caries in elderly patients (142). Herpesviruses have been statistically associated with severe dental caries, but their role, if any, in the caries process remains obscure (38, 212).

An intrafamilial transfer of *S. mutans* was first suggested in the 1980s (23, 47). Transmission of cariogenic bacteria from the mother to the young child is particularly common, although the organisms also may be acquired from a spouse or from outside the family (98). More recent studies have found a similar profile of cariogenic bacteria in young children and their caregivers (186), and molecular typing studies have provided additional evidence of a transmission of mutans streptococci from mother to child (92, 100). Caries-free twins have a more similar oral microflora than twins that are caries-active, and hereditary factors seem to influence the colonization of oral bacterial species that protect against dental caries (41).

The finding of a relatively unique cariogenic microflora has a practical implication. Routine testing for elevated caries risk, based on the salivary level of mutans streptococci (>1,000,000 per ml saliva) and lactobacilli (>100,000 per ml saliva), has been performed in Sweden for more than 30 years (46, 94). Repeat swabbing of teeth of young children with 10% povidone-iodine can reduce the number of mutans streptococci (22) and the incidence of caries (106). Suppression of high levels of *S. mutans* in the mother may delay or prevent the establishment of the organism in her child (91).

## Medical bacteria

A variety of bacterial pathogens of medical diseases can be present in the oral cavity and may be transmitted to individuals in close contact with the host (45). Medical pathogens are mostly detected in the

mouth during the acute phase of the nonoral infection, but the organisms can also occur in the saliva of clinically healthy subjects.

*Streptococcus pyogenes* (beta-hemolytic group A *Streptococcus*) is the cause of a variety of human diseases ranging from mild illnesses of the skin or throat (pharyngitis or 'strep. throat') to severe invasive infections, including necrotizing fasciitis (flesh-eating disease), septicemia, toxic shock syndrome, erysipelas, cellulitis, acute postinfectious glomerulonephritis, rheumatic fever and scarlet fever (178). *S. pyogenes* normally resides in the throat and is one of the most common medical pathogens in the saliva. An asymptomatic carriage stage of *S. pyogenes* was detected in approximately 10% of adults and 25% of children, and in as many as 60% of subjects during large outbreaks of streptococcal pharyngotonsillitis (178). Beta-hemolytic group A streptococci were found in 20% of pharyngeal samples and in 5% of saliva samples of young schoolchildren in New Zealand, with a suggestion of a child-to-child transmission of the organism (185). Members in the same household of a patient with pharyngotonsillitis frequently harbor the same strain of beta-hemolytic group A *Streptococcus*, indicating an intrafamilial transmission of the bacterium (58).

*Haemophilus influenzae* can cause acute bronchitis and exacerbations of chronic obstructive pulmonary disease, as well as meningitis in children and other serious diseases (124). Despite the availability of highly effective vaccines since the early 1990s, 100,000s of unvaccinated children die every year from *H. influenzae*-related disease (208). The organism resides in the pharynx and is rarely recovered from the saliva of healthy individuals (88). It can reach quantities of $10^3$–$10^8$ / ml in the sputum of patients with lower respiratory tract infections and purulent sputum (61).

*Staphylococcus* spp., *Pseudomonas* spp. and *Acinetobacter* spp. are also potential pathogens in respiratory (and other) diseases. These bacteria were detected in the oral cavity of 85% of hospitalized patients in Brazil (216) and in subgingival sites of periodontitis patients in the USA (145, 174). Periodontal staphylococci occurred with highest proportions in younger individuals, and periodontal gram-negative bacilli were found mostly in older subjects (174). Staphylococci can also be prominent in the microbiota of failing dental implants (78). Gram-negative bacilli are frequent inhabitants of the oral cavity of individuals in developing countries, where the bacteria are probably acquired through contaminated potable water (8, 79, 175).

Meningococcal invasive disease (septicemia and / or meningitis in association with hemorrhagic rash) is a life-threatening condition that primarily affects young children. Meningococcal disease can also occur in teenagers, and is more common in collage / university students than in the general population (OR 3.4) (190). Although *Neisseria meningitidis* resides in the nasopharynx and in the tonsils, and is much less common in saliva (129), intimate kissing, especially with multiple partners, constitutes a risk factor for meningococcal disease (OR 3.7) (190). Fortunately, the prevalence of meningitis caused by *N. meningitidis*, *H. influenzae* type b and *Streptococcus pneumoniae* has decreased markedly after the introduction of vaccines against these bacteria (89).

*Neisseria gonorrhoeae* (which causes gonorrhea) and *Treponema pallidum* (which causes syphilis) can produce acute and chronic oral infections. Gonorrhea is a widespread disease worldwide, with an estimated 600,000 new cases each year in the USA (103). Although oral gonorrhea is relatively rare, the literature describes more than 500 cases of oropharyngeal gonorrhea (20). Syphilis is re-emerging in many countries, especially in HIV-infected individuals and among men who have sex with men, and oral sex is often reported to be the route of *T. pallidum* transmission (37, 168, 198). Infants have contracted syphilis by the mouth-to-mouth transfer of pre-chewed food from actively infected relatives (215). Dentists can play an important role in the control of sexually transmitted diseases by identifying signs and symptoms of gonorrhea and syphilis and making appropriate referrals for treatment.

Tuberculosis remains a serious disease worldwide (68). In 2005, there were an estimated 8.8 million new cases of tuberculosis, with 7.4 million occurring in Asia and sub-Saharan Africa, and 1.6 million people died of tuberculosis, including 195,000 with HIV infection (114). *Mycobacterium tuberculosis* can be identified in the whole saliva of almost all tuberculosis patients (54) and of some nontuberculous individuals (101), and has been recovered from alginate dental impressions (140). The US Centers for Disease Control has identified the personnel of a dental-care facility to be at increased risk for infection with *M. tuberculosis* (35) and has updated the tuberculosis infection control guidelines for dental clinics (40).

*Helicobacter pylori* can cause gastritis, peptic ulcers and gastric adenocarcinoma (143). The organism resides primarily in the human stomach and may colonize about 50% of the world's population. Large

quantities of *H. pylori* can be recovered from vomitus, and the bacterium can also be detected in saliva, especially in subjects suffering from gastric ulcer. However, published data on the occurrence of *H. pylori* in the mouth vary greatly (143), perhaps because the oral carriage of *H. pylori* is population dependent or is only transient (50). The transmission route is mainly from the mother, or an older sibling, to younger children. Both gastro-to-oral and oral-to-oral transmission are considered important.

*Legionella pneumophila* is the cause of legionellosis (Legionnaire's disease), a severe type of pneumonia with multisystem failure, and of Pontiac fever, a self-limiting influenza-like illness (114). The natural reservoir for *L. pneumophila* and other *Legionella* species is aquatic habitats. *Legionellae* have been isolated from sputum and other body fluids and sites (123). *L. pneumophila* has also been recovered from dental unit water in England, Germany and Austria (184), and from 8% of dental units in the USA (18). However, no evidence exists to incriminate dental units as a significant source of legionellosis.

## Viruses in saliva

### Herpesviruses

Herpesvirus species comprise the most prevalent viral family in human saliva and are important periodontopathic agents (173). Eight herpesvirus species, with distinct biological and clinical characteristics, can infect humans: herpes simplex virus-1 and -2, varicella-zoster virus, Epstein–Barr virus, human cytomegalovirus, human herpesvirus-6, human herpesvirus-7 and human herpesvirus-8 (Kaposi's sarcoma virus) (171). Herpesviruses establish a lifelong persistent infection, and some herpesvirus species infect as many as 90% of the adult population. The clinical outcome of a herpesvirus infection ranges from subclinical or mild disease to encephalitis, pneumonia and various types of cancer. Herpesviral infections in the oral cavity may give rise to asymptomatic and unrecognized shedding of virions into saliva, or to diseases of the oral mucosa or the periodontium (171, 179). A recent article reviewed acute herpesviral infections in the oral cavity of children (156).

Herpesviruses exhibit a biphasic infection cycle involving a lytic, replicative ('productive') phase and a latent, nonproductive phase (171). The replicative phase involves expression of viral regulatory and structural proteins, and the formation of infectious virion particles (172). The ability to switch between replicative and latent states ensures viral transmissibility between individuals as well as a permanent infection of the host. Following the initial infection, herpesviruses preferentially exist in a state of latency in sensory ganglion cells (herpes simplex viruses and varicella-zoster virus), B-lymphocytes (Epstein–Barr virus, herpesvirus-8), or monocytes and T-lymphocytes (cytomegalovirus and herpesviruses-6 and -7).

Herpesvirus conversion from a latent form to lytic replication can occur spontaneously or be caused by environmental stimuli, chemical agents and physical and psychosocial stress events, as found in adults with an abusive early-childhood history, astronauts in space flight, students before important academic exams, elite athletes in intensive training and subjects with work-related fatigue (Table 1). Re-activation of an oral herpesviral infection can be estimated by a rise in herpesvirus salivary counts or a significant increase in herpesvirus-specific salivary antibodies. Immunocompetent individuals usually experience herpesvirus re-activation lasting for only a few hours or days (112), which is probably too short a time period to initiate or exacerbate clinical disease. However, the egress of herpesvirus virions into saliva poses a risk for infecting individuals in intimate contact.

By contrast, immunosuppressive conditions / diseases and long-term medications may result in the re-activation of oral herpesviruses that continues for an extended period of time and may pose a pathogenetic risk for the infected individual. The immune system of older persons may fail to control a latent varicella-zoster infection, resulting in herpes zoster outbreaks (29), or may not protect effectively against Epstein–Barr virus and cytomegalovirus re-activation (180). The herpesvirus infection in such persons may be characterized as chronically re-activated instead of latent.

The great majority of systemically healthy adults continually shed herpesvirus DNA into saliva. Herpes simplex virus-1 DNA was detected in saliva in quantities up to $2.0–2.8 \times 10^6$ / ml (102, 118). Epstein–Barr virus DNA copies in saliva can reach levels of $10^8$ / ml (76), $1.6 \times 10^9$ / ml (155), $7.1 \times 10^5$ / ml (181) and $2.2 \times 10^6$ per 0.5 μg of DNA (202). As the Epstein–Barr virus salivary count only decreased moderately after large-volume mouth gargles and rinses, or after normal swallowing every 2 min, a large quantity of the virus must constantly enter the saliva (76). However, the salivary Epstein–Barr virus load can vary by as much as 4–5 logs over the course of several months, which complicates the categorizing of

**Table 1.** Salivary herpesviruses and psychosocial stress

| Study | Viral assay | Study population | Study outcome | Comments |
|---|---|---|---|---|
| Shirtcliff et al. (167) | HSV-1 sIgA salivary level | Adolescents who have experienced early deprivation within institutionalized / orphanage settings, or physical abuse during their childhood | Adolescents with early institutional rearing or neglect exhibited higher HSV-1 antibody levels than controls ($P = 0.005$) | Stressful early childhood history may have a lingering effect on HSV-1 re-activation potential |
| Mehta et al. (115) | PCR detection of VZV DNA | Salivary samples from eight astronauts before, during and after space flight | All eight astronauts showed VZV DNA in saliva during and after the space flight; only one astronaut was positive for salivary VZV DNA before the space fight | Stress can induce subclinical re-activation of VZV in saliva |
| Pierson et al. (138) | PCR detection of EBV DNA | Salivary samples from 32 astronauts before, during and after space flight, and from 18 control subjects | The number of EBV DNA copies increased before, during and after space flight compared with non-astronauts | Stress can induce subclinical re-activation of EBV in saliva |
| Payne et al. (136) | PCR detection of EBV DNA | Salivary samples from 11 EBV-seropositive astronauts before, during and after space flight | EBV was detected more frequently before flight than during or after flight | Stress can induce subclinical re-activation of EBV in saliva |
| Uchakin et al. (191) | Real-time PCR detection of salivary EBV DNA | Thirteen adults were subjected to a 4-week bed-rest regime during intravenous hydrocortisone administration | An increase in salivary EBV level of more than 1,000-fold occurred at weeks 3 and 4. EBV returned to pre-study levels after ending the bed rest | Physiological and psychological factors of prolonged bed rest are associated with EBV re-activation. |
| Sarid et al. (159–161) | EBV- and HCMV-specific salivary IgG and IgA | Fifty-four-first-year female students before, during and after two important academic exams | A statistically significant increase was found in the herpesvirus salivary antibody level during the exams compared to the time before and after the exams | Stress during academic exams may give rise to EBV and HCMV re-activation |
| Mehta et al. (116) | PCR detection of EBV DNA | Salivary samples from 16 Antarctic expeditioners during winter isolation | EBV DNA salivary shedding increased ($P = 0.013$) from 6% before or after winter isolation to 13% during the winter period | EBV DNA appeared in saliva more frequently ($P < 0.0005$) at the time of a diminished cell-mediated immune response |
| Gleeson et al. (69) | Salivary anti-EBV IgA monitoring and PCR detection of EBV DNA | Salivary samples from 14 elite swimmers during 30 days of intensive training | EBV DNA was detected in saliva before the appearance of upper-respiratory symptoms in six swimmers | EBV DNA shedding into saliva may be a contributing factor to upper-respiratory illness |
| Kondo (93) | Real-time PCR detection of salivary HHV-6 DNA and HHV-7 DNA | Healthy adults with work-induced fatigue | The salivary copy number of herpesvirus DNA increased with fatigue and declined during holidays | Work-induced fatigue may re-activate herpesviruses |

EBV, Epstein–Barr virus; HCMV, human cytomegalovirus; HHV, human herpesvirus; HSV, herpes simplex virus; IgA, immunoglobulin A; IgG, immunoglobulin G; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

individuals as low, intermediate or high viral shedders (76). Cytomegalovirus DNA was detected in the saliva of 61% of immunocompetent and immunocompromised subjects (65), and could reach salivary DNA copy counts of $4.2 \times 10^4$ / ml (155). Herpesvirus-6 and herpesvirus-7 may occur in saliva, with prevalences exceeding 95% and in quantities of several million DNA copies / ml (118). Salivary herpesvirus-8 DNA, in quantities of 2.0–7.3 $\log_{10}$ copies / ml, was detected in 61% of asymptomatic, immunocompetent men who have sex with men (32), and in 37% of Zimbabwean women with Kaposi's sarcoma, but not in women without the disease (99). Varicella-zoster virus DNA is present at a low prevalence and in quantities of <1,100 copies / ml in the saliva of both healthy and HIV-infected individuals (205).

Table 2 shows the association between salivary herpesviruses and periodontitis. A periodontal dual infection of herpesviruses and pathogenic bacteria gives rise to enhanced cytokine release and immune signaling dysregulation (27, 104, 187), and tends to be associated with more severe periodontitis than a periodontal infection involving solely bacteria (172). Herpes simplex virus-1 may contribute to periodontitis in a subset of individuals (173), and the virus was identified in whole saliva of 24% of patients with chronic periodontitis (71). In the same group of patients, herpes simplex virus-1 DNA was present in 16% of subgingival samples and in 8% of peripheral blood samples (71). Herpes simplex virus DNA was found in the saliva of 84% of patients with overt herpetic lesions (144). Epstein–Barr virus DNA has been detected in whole saliva of 79% of periodontitis patients and 33% of gingivitis patients (155), and in 49% of periodontitis patients and 15% of healthy individuals (82). A correlation was found between salivary and subgingival levels of Epstein–Barr virus in one study (48) but not in another study (84). As high quantities of salivary Epstein–Barr virus DNA can be recovered from fully edentulous patients (155), the occurrence of the virus in saliva may not be a reliable indicator of its subgingival level or of the periodontitis disease status. Cytomegalovirus periodontal active infection is closely linked to aggressive periodontitis (173). Cytomegalovirus DNA was detected in the saliva of 50% of periodontitis patients, but was not found in the saliva of gingivitis patients or complete denture wearers, suggesting that salivary cytomegalovirus originates mainly from periodontitis lesions (155). Also, cytomegalovirus DNA from infected breast milk appeared in the saliva of infants at 4 months of age, peaked 4–10 months after birth, and thereafter decreased or became undetectable (122). To sum up, a great proportion of salivary herpeviruses are shed from periodontal disease sites. As periodontal treatment can markedly reduce subgingival (73, 162) and salivary (82, 162) herpesvirus DNA counts, the establishment of a healthy periodontium may diminish the risk of intersubject herpesvirus transmission and of herpesvirus-related diseases. The close relationship between some herpesvirus species and periodontitis also argues for examining the potential of using herpesvirus salivary counts to indicate periodontal disease risk.

Infectious mononucleosis is caused by a primary infection with Epstein–Barr virus, and predominantly by Epstein–Barr virus type 1 (44). Approximately 10% of mononucleosis-like disease is attributable to cytomegalovirus. The Epstein–Barr virus infects B-lymphocytes, which gives rise to the strong T-lymphocyte response that is characteristic of mononucleosis. Clinical signs of infectious mononucleosis are long-lasting fever, tonsillopharyngitis, lymphadenopathy, fatigue, and occasionally splenomegaly, liver involvement and pericarditis (199). Oral signs are sore throat, palatal petechiae and enlarged lymph nodes in the throat and neck. The Epstein–Barr virus is transmitted through direct contact with virus-infected saliva, such as with kissing, and rarely via the air or blood. Young adults with a primary Epstein–Barr virus infection can rapidly clear the virus from the blood but not from the oropharynx (19). However, individuals who are already infected with the Epstein–Barr virus (and cytomegalovirus) are not at risk for infectious mononucleosis, even when exposed to individuals with the disease.

Other diseases have been linked to salivary herpesviruses (Table 2). Relationships have been found between Bell's palsy (idiopathic peripheral facial paralysis) and an active herpes simplex virus-1 infection (3), between oropharyngeal lesions of the Ramsay Hunt syndrome and varicella-zoster virus (62, 144), and between HIV infection and Epstein–Barr virus (74) and herpesvirus-8 (33). Young children with exanthem subitum acquired the disease from their mothers who excreted the causative herpesvirus-6 into saliva (121).

Human immunodeficiency virus infection is a potent herpesvirus re-activator, as demonstrated by a strong correlation between decreasing CD4 cell counts in HIV-infected patients and increasing rates of herpesvirus re-activation (34). An HIV infection is frequently associated with the salivary presence of several re-activated herpesvirus species (Table 3). In the mode of synergism, herpesviruses (196), *P. gingivalis* (83) and other periodontal bacteria (81) may

**Table 2.** Salivary herpesviruses and oral diseases

| Study | Disease | Study material and methods | Study outcome | Comments |
|---|---|---|---|---|
| Şahin et al. (155) | Periodontitis | Whole saliva was collected from 14 systemically healthy periodontitis patients, 15 gingivitis patients and 13 complete denture wearers. Real-time TaqMan PCR was used for detection of HCMV and EBV DNAs | Salivary HCMV (range, $3.3 \times 10^3$–$4.2 \times 10^4$/ml) was detected in seven (50%) periodontitis patients, but not in any gingivitis or edentulous subjects ($P < 0.001$). Salivary EBV (range, $3.6 \times 10^2$–$1.6 \times 10^9$/ml) was detected in 11 (79%) periodontitis patients, in five (33%) gingivitis patients and in seven (54%) edentulous subjects ($P = 0.076$) | Periodontitis lesions seem to constitute the main origin of salivary HCMV, but do not comprise the sole source of salivary EBV |
| Dawson et al. (48) | Periodontitis | Samples of whole saliva and subgingival plaque were collected from 65 adults with chronic periodontitis. Real-time PCR detection of EBV DNA | Patients exhibiting EBV DNA in saliva were 10 times more likely to have EBV DNA in subgingival plaque than patients lacking EBV DNA in saliva (odds ratio = 10.1, $P = 0.0009$) | The presence of EBV DNA in saliva and subgingival plaque showed correlation with each other but not with periodontal disease severity |
| Imbronito et al. (84) | Periodontitis | Samples of whole saliva and of subgingival plaque were collected from 40 adults with chronic periodontitis. Nested PCR was used to detect EBV DNA and HCMV DNA | EBV-1 DNA was detected in 45% of subgingival samples and in 38% of salivary samples. HCMV DNA was detected in 83% of subgingival samples and in 75% of salivary samples | The sensitivity for viral detection in saliva compared with subgingival plaque was low for EBV DNA (22%) and high for HCMV DNA (82%). Oral detection of EBV DNA may require both salivary and subgingival sampling |
| Sugano et al. (181) | Periodontitis | Salivary samples of 33 systemically healthy periodontitis patients, 25–68 years of age. Real-time PCR was used to detect EBV DNA and *Porphyromonas gingivalis* | Forty-nine percent of patients harbored salivary EBV DNA at a concentration of $4.48 \pm 2.19 \times 10^5$/ml. EBV-positive patients showed higher mean salivary proportion of *P. gingivalis* than EBV-negative patients | *P. gingivalis* sonicate was able to re-activate EBV, and *P. gingivalis*–EBV synergistic interaction may play a pathogenetic role in periodontitis |
| Raggam et al. (144) | Herpetic lesions | Salivary samples from 25 patients with herpetic lesions. Quantification of HSV DNA was based on liquid phase-based saliva collection and an automated commercial molecular assay | Nineteen samples yielded HSV-1 DNA (range, $1.2 \times 10^4$–$2.1 \times 10^5$ copies/ml) and two samples yielded HSV-2 DNA (range, $1.4 \times 10^3$–$2.2 \times 10^4$ copies/ml) | A fully automated diagnostic system may be useful in identifying saliva-borne viruses |

**Table 2.** (Continued)

| Study | Disease | Study material and methods | Study outcome | Comments |
|---|---|---|---|---|
| Crawford et al. (44) | Infectious mononucleosis | Two-hundred and forty-one college students who were EBV-seronegative at the time of entering college were followed-up for 3 years | The annual EBV seroconversion rate was 15.2% and the annual mononucleosis rate was 3.7%. The seroconversion rate was 28% for students who had oral sex and 13% for students who did not (not significant) | Having a greater number of sex partners was a highly significant risk factor for EBV seropositivity |
| Abiko et al. (3) | Bell's palsy | Sixteen patients with Bell's palsy provided repeat samples of submandibular and parotid saliva from the affected and from the unaffected side. PCR detection of HSV-1 DNA was carried out | Five patients (31%) showed a high detection rate of HSV DNA for up to 2 weeks after disease onset from the affected side, but a low HSV DNA detection rate from the unaffected side | HSV-1 re-activation may be a pathogenic factor in some cases of Bell's palsy |
| Furuta et al. (62, 63) | Ramsay Hunt syndrome | Forty-seven patients with the Ramsay Hunt syndrome. Real-time PCR detection of VZV DNA | Patients with oropharyngeal herpes zoster lesions had a VZV DNA salivary load that was about 10,000 copies higher than patients with herpes zoster lesions of the skin. The salivary VZV copy number ranged from 38 to $1.3 \times 10^6$ copies / 50 μl | The VZV DNA level in saliva seems to reflect the kinetics of VZV re-activation in the facial nerve |
| Raggam et al. (144) | Ramsay Hunt syndrome | Ten patients with Ramsay Hunt syndrome. Quantification of VZV DNA was based on liquid phase-based saliva collection and on an automated commercial molecular assay | Seven salivary samples (70%) yielded VZV DNA (range, $3.3 \times 10^4$–$5.8 \times 10^5$ copies / ml) | A fully automated diagnostic system may be useful in identifying saliva-borne viruses |
| Griffen et al. (74) | HIV infection | Forty-one HIV-1 seropositive persons provided daily swabs from gingiva, buccal mucosa and palate for a median of 61 consecutive days. PCR was used to detect HSV-1, HSV-2, EBV and HCMV DNAs | Persons with high EBV DNA shedding rates showed salivary HCMV DNA significantly more often than persons with low EBV DNA shedding rates. HSV DNA oral shedding was observed least frequently | Salivary shedding of herpesviruses was common even in HAART-treated patients |

EBV, Epstein–Barr virus; HAART, highly active antiretroviral therapy; HCMV, human cytomegalovirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; MMR, measles, mumps and rubella; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

also activate a latent HIV infection. Human immunodeficiency virus-infected individuals who either received or did not receive highly active antiretroviral therapy (HAART) were found to have a similar rate and quantity of oral shedding of herpes simplex virus, Epstein–Barr virus and cytomegalovirus (74). Subjects not on HAART exhibited a moderately higher shedding of oral herpesvirus-8 (33). Herpesvirus-8

**Table 3.** Salivary herpesviruses and immunosuppressive diseases and medications

| Study | Condition / disease | Study material and methods | Study outcome | Comments |
|---|---|---|---|---|
| Griffen et al. (74) | HIV infection | Forty-one HIV-1 seropositive persons provided daily swabs from gingiva, buccal mucosa and palate for a median of 61 consecutive days. PCR was used to detect HSV-1, HSV-2, EBV and HCMV DNAs | HSV DNA was detected in saliva in 5% of days, HCMV DNA in 19% of days and EBV DNA in 71% of days. The median DNA copies per ml of HSV, HCMV and EBV were $10^{4.0}$, $10^{3.3}$ and $10^{5.3}$, respectively | Salivary shedding of herpesviruses was common, even among HAART-treated patients |
| Pauk et al. (134) | HIV infection | HHV-8 DNA was detected by PCR in saliva and in oral swabs obtained daily from 23 HHV-8-seropositive men who had sex with men | HHV-8 DNA was detected in 34% of oropharyngeal samples (382 of 1134), in 0.4% of urethral samples (3 of 848) and in 1% of anal samples (14 of 1087) | Oral exposure to infectious saliva is a potential risk factor for the acquisition of HHV-8 among men who have sex with men |
| Kim et al. (90) | HIV infection | One-hundred and nine HSV-2-seropositive men (50 HIV positive and 59 HIV negative) provided oral swabs for 64 consecutive days. PCR was used to detect HSV-2 DNA in saliva | HSV-2 DNA was detected from oral swabs in 40% of the subjects on at least 1 day. HIV-positive men shed HSV-2 DNA orally more frequently than HIV-negative men (odds ratio, 2.7) | HSV-2 oral re-activation was common, especially in HIV-positive men, was always asymptomatic and often occurred on days of genital HSV-2 re-activation |
| Miller et al. (119) | HIV infection | Fifty-eight HIV-seropositive individuals in a case–control study. PCR was used to detect various herpesvirus DNAs in saliva | Salivary DNA of EBV, HHV-8, HCMV and HSV-1 was detected in 90%, 57%, 31% and 16%, respectively, of HIV-positive subjects, and in 48%, 24%, 2% and 2%, respectively, of HIV-negative subjects | HHVs were significantly more prevalent in the saliva of HIV-seropositive subjects (odds ratios, 4.2–26.2). Saliva of HIV-infected persons is a potential risk factor for transmission of multiple HHVs |
| Fidouh-Houhou et al. (59) | HIV infection | Ninety-eight HIV-infected subjects with no history of HCMV disease. PCR was used for detection of HCMV DNA in saliva | Prior salivary shedding of HCMV DNA was associated with a high risk of developing HCMV disease ($P = 0.04$) | HIV-related immunosuppression can re-active a latent HCMV infection and cause clinical HCMV infections |
| Lucht et al. (109) | HIV infection / oral hairy leukoplakia (OHL) | Fifteen HIV-1-infected subjects with OHL and 45 HIV-1-infected subjects without OHL. PCR was used to detect EBV DNA in saliva | All 15 patients with OHL demonstrated EBV DNA oral shedding, whereas only 35 (78%) subjects without OHL revealed salivary EBV DNA ($P = 0.04$) | Increased excretion of EBV in saliva occurs soon after the primary HIV-1 infection, and OHL may occur early on during the HIV-1 infection |

resides in the buccal epithelial cells of HIV-infected subjects (134), and can be transmitted horizontally from an HIV-infected mother to her young children (66, 111) but, despite the possibility of *in utero* infection (28), vertical transmission of the virus is uncommon in infants born to an HIV-positive mother (111). Herpesvirus-8 can also be transmitted by oral sex. Deep kissing was an independent risk factor (odds ratio of 5.4) for transmitting herpesvirus-8 from HIV-seropositive men to HIV-seronegative men,

**Table 3.** (Continued)

| Study | Condition / disease | Study material and methods | Study outcome | Comments |
|---|---|---|---|---|
| Lucht et al. (110) | HIV infection | Forty-four HIV-infected and 15 healthy HIV-seronegative subjects. PCR was used to detect DNA of HCMV, HHV-6, HHV-7, and HHV-8 in saliva | HCMV DNA was found most often in patients with AIDS. HHV-8 DNA was found only in symptomatic HIV-1-infected patients (33%). Oral shedding of HHV-6 and HHV-7 was not elevated in HIV-infected subjects | Oral shedding of HCMV DNA and HHV-8 DNA correlated positively with the severity of the HIV-associated immunodeficiency |
| Di Luca et al. (51) | Common cold, recurrent aphthous ulceration, HIV infection | Sixteen subjects with the common cold, 12 subjects with recurrent aphthous ulceration and 26 HIV-infected subjects. PCR was used to detect HHV-6 DNA and HHV-7 DNA in saliva | Salivary HHV-7 DNA was detected in 55% of healthy individuals, in 56% of individuals with the common cold, in 66% with recurrent aphthous ulcers and in 81% with HIV infection. HHV-6 DNA was detected only in a few salivary specimens | HHV-7 undergoes an active replication in salivary glands and sheds infectious virions into saliva, especially in HIV-infected subjects |
| Rhinow et al. (148) | Bone marrow and stem cell transplantation | Unstimulated saliva from 20 patients before, during and after bone marrow and stem cell transplantation. PCR was used to detect HCMV | Salivary HCMV counts post-transplantation showed evidence of HCMV re-activation. HCMV infection from the transplant donor was not observed | Transplantation procedures may re-active a latent HCMV infection |
| Al-Otaibi et al. (9) | Renal allograft recipient | A 33-year-old renal allograft recipient provided pre- and post-transplantation salivary samples. Real-time PCR detection of HHV-8 | HHV-8 showed salivary loads of $2.6 \times 10^6$–$4.1 \times 10^6$ genome-copies / ml | Post-transplantation, the salivary HHV-8 DNA load declined precipitously following an increase in the dosage of valacyclovir |

AIDS, acquired immunodeficiency syndrome; EBV, Epstein–Barr virus; HAART, highly active antiretroviral therapy; HCMV, human cytomegalovirus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

and the mean load of herpesvirus-8 DNA in saliva (4.3 log copies / ml) and pharyngeal swabs (3.1 log copies / ml) was approximately 2.5 times higher than those of genital tract samples or anal swabs (134). Taken together, the saliva of HIV-infected persons is a risk factor for the transmission of several virulent herpesvirus species, and patients receiving HAART cannot be assumed to be less infectious for herpesviruses than individuals not receiving HAART.

Oral mucositis is an important complication of immunosuppressive radiotherapy, chemotherapy and radiochemotherapy (163). The mucositis may involve herpesviruses, bacteria and yeasts, individually or in combination (163). Bone marrow and stem cell transplantation has been associated with oral cytomegalovirus re-activation (148), and renal allograft transplantation has been associated with oral cytomegalovirus re-activation (128) and oral herpesvirus-8 re-activation (9). Also, although not studied in the oral cavity, corticosteroid immunosuppressive treatment may trigger the re-activation of herpesvirus species (14, 49, 164, 211).

## Other viruses

Viruses of serious medical diseases can be present in saliva at levels sufficient to be transmitted from person to person through close (within 2 meter) or intimate contact (Table 4). Moreover, viral pathogens can be transferred to humans by animals or insects (Table 4), or from humans to animals and then later

transferred back into humans (56). Viruses in saliva may infect the periodontium and exacerbate periodontal disease.

Human papillomaviruses are frequent inhabitants of the oral mucosa of normal adults (188) and have been found to occur in the saliva of 25% of healthy individuals (154). Papillomavirus DNA was detected in 26% of gingival biopsies from periodontitis lesions (80), and in as many as 92% of biopsies of cyclosporin-induced gingival hyperplasia from renal transplant recipients (30). Papillomavirus type 16 is associated with a subset of oropharyngeal squamous cell carcinomas (171), and quantitative measurement of salivary papillomavirus-16 DNA has shown promise for early detection of recurrence of head and neck squamous cell carcinoma (39), and for surveillance of premalignant oral disorders (183). Papillomavirus DNA was identified in the saliva of 10% (5) and 41% (154) of oral squamous cell carcinoma patients, and in the saliva of 35% of HIV-positive individuals (5). A spouse had a 10-fold higher risk of acquiring a persistent oral papillomavirus infection if the other spouse had a persistent oral papillomavirus infection, a finding that is consistent with the oral route of papillomavirus transmission (149). The likelihood of contracting an oral papillomavirus infection increases with increasing numbers of open-mouthed kissing partners and oral sex partners (52), and papillomavirus-positive oral tumors are strongly linked to multiple oral sex partners (53). The current prophylactic papillomavirus-6/11/16/18 vaccine, designed to prevent cervical cancer, generates an oral antibody response and will probably also reduce the incidence of papillomavirus-related diseases of the mouth (153).

Human immunodeficiency virus is transmitted through sexual contact or by contaminated needles and blood, but only exceptionally rarely through saliva. A recent study provided compelling evidence that three infants acquired HIV/acquired immunedeficiency syndrome (AIDS) after receiving prechewed food (64). The HIV-infected caregivers had bleeding gingiva while masticating food for the infants, and thus blood, not saliva, was probably the vehicle for HIV transmission in the three cases reported. In fact, submandibular/sublingual gland secretions contain mucin molecules that normally will prevent infection and transmission of HIV by the oral route (75). Thus, as is the case for HIV and for other viruses, saliva is not merely serving as a passive transport medium, but can significantly affect the efficiency of pathogen transmission and the course of disease. Fortunately, anti-retroviral drugs have turned HIV infection into a manageable condition with a greatly reduced morbidity.

The proviral DNA of human T-cell lymphotropic virus type I, an oncogenic retrovirus, was detected in whole saliva of 77% of Mashhadi-born Iranian Jews with viral myelopathy (4). This finding may suggest the potential for a salivary transmission of human T-cell lymphotropic virus type I and may possibly help to explain the relatively high rate of myelopathy in the elderly Mashhadi-Jewish population. The human T-cell lymphotropic virus type I can also be present in the saliva of asymptomatic carriers of the virus (4).

Hepatitis viruses (designated A through G) cause the majority of cases of acute and chronic hepatitis and liver damage worldwide. Hepatitis ranges pathologically from asymptomatic or mild disease to fulminant liver failure. Hepatitis A and hepatitis E viruses are transmitted by water contaminated with feces (fecal–oral route), produce acute infections and do not induce a chronic carrier state. A high incidence of hepatitis A and hepatitis E viral infections occurs in countries with poor sanitary standards. Hepatitis A virus RNA was detected in the saliva of 50% of patients during a hepatitis A outbreak (11). A study in cynomolgus monkeys found that the tonsils and salivary glands acted as extrahepatic sites for early hepatitis A virus replication and constituted potential sources for saliva-transmitted infection (10). Hepatitis B virus is parenterally transmitted and is frequently associated with chronic viremia. Hepatitis B virus DNA was found at concentrations of $>10^5$ copies/ml of saliva in 15% of patients with chronic hepatitis B (195). That concentration may be sufficient to permit horizontal transmission of the virus, and perhaps some of the 20% of hepatitis B patients, who contract the disease without a known origin of the infection, may have acquired the hepatitis B virus by salivary transfer (195). Chronic hepatitis C affects more than 170 million people worldwide, and the hepatitis C virus persists in 80% of the infected individuals, where it can give rise to liver inflammation, liver cirrhosis and hepatocellular carcinoma (135), and perhaps to periodontitis, Sjögren's syndrome, oral lichen planus and sialadenitis (171). Hepatitis C virus RNA was present in the saliva of 39–72% of subjects with chronic hepatitis (113, 133, 144, 204), and was detected in 59% of gingival crevice fluid specimens from viremic patients (113). The gingival crevice fluid was identified as the major source for salivary hepatitis C virus (113). Twenty-seven percent of spouses of individuals with chronic hepatitis C revealed antibodies against

**Table 4.** Salivary viruses and medical diseases

| Virus | Disease | Findings and comments | Study |
|---|---|---|---|
| Human papillomavirus (HPV) | Cervical cancer and oropharyngeal squamous cell carcinoma | Papillomavirus DNA was identified in the saliva of 10% and 41% of oral squamous cell carcinoma patients | Adamopoulou et al. (5), SahebJamee et al. (154) |
| Human immunodeficiency virus (HIV) | Three HIV-positive infants (9–39 months old) were fed with premasticated food: two children by an HIV-infected mother with oral bleeding; and one child by an HIV-positive aunt (the mother was HIV-negative) | The infants were not breastfed and perinatal transmission of HIV was previously ruled out. Premasticative feeding practice may lead to late postnatal HIV infection if performed by an HIV-infected caregiver | Gaur et al. (64) |
| Human T-cell lymphotropic virus type I (HTLV-I) | Thirteen Mashhadi-born Iranian Jews with HTLV-I-associated myelopathy/spastic paraparesis | Proviral HTLV-I DNA was detected by mouthwash PCR and by HTLV-I probe in 71% of HTLV-I infected subjects but in none of healthy controls | Achiron et al. (4) |
| Acute hepatitis A virus (HAV) infection | Seventy-one subjects with HAV outbreak | HAV RNA was detected in 50% of salivary samples | Amado et al. (11) |
| Chronic hepatitis B virus (HBV) infection | One-hundred and fifty subjects with chronic HBV infection | 15% of the HBV carriers showed salivary HBV DNA of $>10^5$ copies/ml, suggesting a potential horizontal transmission by saliva | van der Eijk et al. (195) |
| Chronic hepatitis C virus (HCV) infection | Subjects with chronic HCV infection | 72% of 474, 48% of 40, 39% of 46, 39% of 80 and 37% of 59 salivary samples yielded HCV RNA. Salivary HCV RNA levels ranged from $7.5 \times 10^2$ to $1.8 \times 10^3$ IU/ml (144), and averaged $1.15 \times 10^6$ in HIV-infected subjects (147) | Wang et al. (204), Raggam et al. (144), Pastore et al. (133), Shafique et al. (166), Rey et al. (147) |
| Chronic hepatitis G virus (HGV) infection | Thirty subjects with chronic HGV infection | HGV RNA was detected in 6.6% of salivary samples | Eugenia et al. (57) |
| Respiratory syncytial virus, parainfluenza virus, influenza virus and adenovirus | Lower respiratory tract clinical infection | Test viruses were detected in 74% of salivary specimens and in 77% of nasopharyngeal specimens (the gold standard) | Robinson et al. (150) |
| Severe acute respiratory syndrome (SARS) corona virus | Seventeen probable SARS-case patients | The SARS virus was detected in the saliva of all 17 patients in quantities of $7.08 \times 10^3$–$6.38 \times 10^8$ copies/ml | Wang et al. (203) |
| Merkel cell carcinoma (MCC) virus (polyomavirus) | MCC is a highly lethal primary neuroepithelial tumor of the skin with predominance in patients with cell-mediated immune deficiency | MCC virus can occur at relatively high levels in the saliva of MCC patients | Loyo et al. (107) |
| BK polyomavirus | BK virus is urotheliotropic and can cause interstitial nephritis, which is associated with a high rate of renal allograft loss | BK virus DNA can occur with salivary copy numbers of $10^4$/ml in HIV-infected individuals and $10^2$/ml in HIV-negative individuals | Boothbur & Brennan (25), Jeffers et al. (86) |

**Table 4.** (Continued)

| Virus | Disease | Findings and comments | Study |
|---|---|---|---|
| Measles virus (paramyxovirus) | Salivary samples from 55 measles outbreak cases in Ethiopia | Hundred percent of salivary samples from measles patients were positive for measles virus RNA | Nigatu et al. (126) |
| Rubella (German measles) virus (togavirus) | Rubella outbreak in Perú | Reverse transcription-PCR examination of oral fluid identified more rubella cases than IgM testing of either serum or oral fluid samples in the first 2 days after the onset of rash | Abernathy et al. (2) |
| Ebola virus (filovirus) hemorrhagic fever | Ebola is an acute viral infection with fever and bleeding diathesis, and with a 50–100% mortality rate | Twenty-four patients with Ebola-positive serum revealed Ebola viral copies in saliva | Formenty et al. (60) |
| Rabies virus, a rhabdovirus with a reservoir in dogs, foxes, cats, vampire bats and other animals | Rabies is a central nervous system disease that untreated is almost invariably fatal | Rabies virus was detected in 88% of salivary samples of patients with an ante-mortem diagnosis of rabies | Nagaraj et al. (125) |
| Hantaviruses (Bunyaviridae family; rodent viruses infecting humans) | Hantaviruses can cause hemorrhagic fever with renal syndrome (in Eurasia) or cardiopulmonary syndrome (in the Americas). Rodent-to-human transmission usually occurs by the inhalation of aerosolized virus-contaminated rodent excreta | The Andes hantavirus resides in the secretory cells of human salivary glands and may exhibit human-to-human transmission. Hantavirus RNA was detected in the saliva after the onset of disease symptoms | Hardestam et al. (77), Pettersson et al. (137) |
| Dengue virus, a mosquito-borne flavivirus | Dengue fever and the potentially fatal dengue hemorrhagic fever occur in tropical and subtropical countries | The dengue virus genome was detected in saliva and urine from patients with acute dengue fever | Mizuno et al. (120), Poloni et al. (141) |
| Nipah virus, a paramyxovirus with a reservoir in fruit bats | The Nipah virus introduced into humans can cause severe encephalitis and respiratory disease | Fifty percent of Nipah virus patients in Bangladesh developed disease following person-to-person salivary transmission of the virus | Luby et al. (108) |
| Crimean-Congo hemorrhagic fever (CCHF) virus (nairovirus; a tick-borne virus) | CCHF is an acute infection with a high case-fatality rate | The genome of the CCHF virus was detected in the saliva of five of six patients with confirmed CCHF | Bodur et al. (24) |

the virus (6), pointing to an intrafamilial, but not necessarily a sexual, mode of transmission of the virus (31). Toothbrushes used by hepatitis C patients can contain the virus and should not be utilized by other members of a family (7, 105). Hepatitis G virus RNA was detected in 7% of salivary samples from individuals with chronic hepatitis G (57).

Viruses of respiratory diseases are usually transmitted through coughs or sneezes that release large quantities of high-velocity droplets into the air, and the risk of cross-infection through salivary exchange is comparatively small. Children with respiratory disease revealed respiratory viruses (respiratory syncytial virus, influenza virus, parainfluenza virus, adenovirus) in 74% of oral specimens and in 77% of nasopharyngeal specimens (150), and respiratory syncytial virus RNA in 76% of salivary samples (201). Although present in saliva (150), influenza virions may not be infectious because of the anti-influenza virus activity of salivary glycoproteins (207). The severe acute respiratory syndrome (SARS) corona virus, the etiological agent of a highly lethal type of

pneumonia, was detected in the saliva of each SARS patient studied, and was present in quantities up to $6.38 \times 10^8$ copies / ml (203). A dental clinic located in a SARS-affected region must institute strict infection-control measures in order to prevent cross-infection with the SARS virus (158).

Measles and rubella are rare diseases in vaccinated populations, but still occur in unvaccinated persons, commonly in developing countries. The causative viruses are spread through respiration, and can be present in saliva in high numbers during disease outbreaks (2, 126). Ebola is a viral hemorrhagic febrile disease that can cause death in 2–5 days. Ebola virus was detected in the saliva of all 24 patients with a positive Ebola diagnosis (60), and transmission of the Ebola virus through oral exposure has been demonstrated in nonhuman primates (85). Merkel cell carcinoma is a highly lethal neuroepithelial tumor of the skin, and at least some Merkel cell carcinomas appear to be caused by a newly discovered polyomavirus. The Merkel cell polyomavirus is found in relatively high numbers in respiratory secretions and in the saliva of patients with Merkel cell carcinoma (107), possibly exposing close individuals to a risk of infection.

Humans can contract serious viral diseases through zoonotic transfer (Table 4). The rabies virus resides in dogs, foxes, cats, vampire bats and other animals, and is transmitted to humans through the bite of a rabid animal. Rabies virus RNA was identified in 88% of salivary samples from humans with an ante-mortem diagnosis of rabies (125). Hantaviruses cause hemorrhagic fever with renal syndrome (in Eurasia) or cardiopulmonary syndrome (in the Americas), and rodent-to-human transmission usually occurs by the inhalation of aerozolized virus-contaminated rodent excreta. However, the Andes hantavirus infects the secretory cells of human salivary glands and can be detected in the saliva after onset of disease symptoms, suggesting that the virus also may be transmitted by human-to-human contact (77, 137). Nipah virus, a paramyxovirus with a reservoir in fruit bats, can cause respiratory disease and severe encephalitis in humans. A study in Bangladesh concluded that 50% of Nipah patients acquired the virus through salivary transmission from person to person (108).

Some viral diseases in tropical and subtropical parts of the world are acquired through insect bites. Dengue fever, caused by a mosquito-borne flavivirus, afflicts more than 100 million subjects annually. Patients with dengue fever revealed the dengue virus genome in saliva during the acute phase of the infection (120, 141). Crimean-Congo hemorrhagic fever virus is transmitted by tick bites or by contact with the blood or tissues of infected patients and livestock. The genome of the Crimean-Congo hemorrhagic fever virus was detected in the saliva of five of six patients with confirmed disease (24), increasing the likelihood of a human-to-human transmission.

## Perspectives

Our knowledge of infectious agents in the human oral cavity has expanded greatly in recent years, mainly as a result of molecular techniques that can identify and quantify oral bacteria and viruses with great accuracy. Several oral and medical pathogens occur in saliva at levels that are sufficient to infect close individuals, and contact with saliva may be a more important mode of pathogen transmission than previously realized. The rising awareness of the infectious potential of saliva raises challenging questions about the safety of intimate ('deep' or 'open mouthed') kissing contact. The risk of cross-infection by salivary transfer may not be trivial and needs to be studied further. The type of pathogenic agents that can retain infectiousness in saliva and that are efficiently spread by saliva needs to be identified and controlled.

Current knowledge of the oral ecology may form the basis for more efficient treatments of bacterial and viral infections around teeth and of the oral mucosa. The finding of major periodontopathic bacteria in nondental sites, especially on the tongue, argues for antimicrobial treatment of the entire oral cavity, not only of dental biofilms (151). Virtually all periodontal patients can benefit from treatment with antiseptics active against bacteria and herpesviruses, such as sodium hypochlorite and povidone-iodine (169), and selective patients may benefit from treatment with systemic antibacterial (170) and antiviral (182) medications. Effective periodontal therapy includes professional administration of a battery of well-tolerated antimicrobial agents, each exhibiting high activity against periodontal pathogens and delivered in ways that simultaneously affect pathogens residing in different oral ecological niches [i.e. chlorhexidine or dilute sodium hypochlorite (bleach) for general oral disinfection, povidone-iodine for subgingival irrigation, and systemic antibiotics to reach microorganisms within periodontal tissue and in difficult-to-reach subgingival and extra-dental sites]. The follow-up maintenance program should

have a strong anti-infective emphasis, and may include patient-administered subgingival irrigation with dilute sodium hypochlorite and oral rinsing with sodium hypochlorite or chlorhexidine two to three times per week. Full-mouth disinfection may also reduce the risk for cross-infection of oral pathogens between individuals in close contact.

However, in the final analysis, most chronic infectious diseases such as periodontitis and dental caries will be defeated on a mass-scale only by employing effective, safe and inexpensive vaccines. Vaccines may be prophylactic, therapeutic, or a combination of both. Perhaps a vaccine that reduces the infectious load without actually eliminating the infectious agent is sufficient to arrest or prevent dental and other oral diseases. Vaccination studies on herpesviruses and some oral bacteria have yielded occasional successes in animal models, but a number of human trials have failed to show adequate efficacy. Vaccine development has been difficult because of the heterogeneity, variability and poor immunogenicity of the outer surface components of many infectious agents. Nonetheless, despite the setbacks, vaccines against herpes zoster virus and oncogenic papillomaviruses were recently approved for clinical use by the US Food and Drug Administration. Effective and safe vaccines against oral infectious diseases constitute one of the most important needs in dentistry.

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