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 1

Infection Transmission by Saliva and the Paradoxical Protective Role of Saliva

1.1 SALIVA COMPOSITION AND SECRETION

Saliva is produced by both major (parotid and submandibular and sublingual) and minor (located in the mouth) glands, with different constituents and properties between the two groups. In the mouth saliva is a colorless, odorless, tasteless, watery liquid containing 99% water and 1% organic and inorganic substances and dissolved gases, mainly oxygen and carbon dioxide. Salivary constituents can be grouped into proteins (e.g., amylase and lysozyme), organic molecules (e.g., urea, lipids, and glucose mainly), and electrolytes (e.g., sodium, calcium, chlorine, and phosphates).[1] Cellular elements such as epithelial cells, leucocytes and various hormones, and vitamins have also been detected. The composition of saliva is modified, depending on factors such as secreted amount, circadian rhythm, duration and nature of stimuli, diet, and medication intake, among others.

Despite this heterogeneous composition, from the functional point of view saliva has to be considered as a unique biological fluid, and not as the sum of its biochemical components.[2,3]

Salivary secretion and maintenance of a film of saliva on oral surfaces is dependent upon nerve-mediated, reflex salivary gland secretion mainly stimulated by taste. The afferent arm is mainly activated by stimulation of chemoreceptors (located in the taste buds) and mechanoreceptors (located in the periodontal ligament).[4] Olfaction, mental processes, and stretch of the stomach are weak stimuli. Impulses affecting secretion depending on the emotional state are carried by afferent cranial nerves V, VII, IX, and X to the CNS salivary nuclei (salivation center) in the medulla oblongata. The efferent part of the reflex is mainly parasympathetic. The cranial nerve VII provides control of the submandibular, sublingual, and minor glands, whereas the cranial nerve IX controls the parotid glands. The flow of saliva is enhanced

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by sympathetic innervation, which promotes contraction of muscle fibers around the salivary ducts.[5] Autonomic nerves also have an important role in both gland development and function.[6] A dry mouth is a common experience where there is fear.

Saliva may be secreted in the absence of exogenous stimuli, then referred to as the resting or unstimulated salivary flow. In the resting state 70% of saliva is secreted by the submandibular and sublingual glands. When stimulated, the parotids provide most of the saliva and flow can increase by up to fivefold. On average, in healthy nonmedicated adults, the unstimulated and chewing-stimulated salivary flow rates are about 0.3 and 1.5 mL/min respectively,[1] but the range is wide and the limits of normality in all age groups and both genders are considerable. The normal daily production of saliva varies from 700 mL to 1.5 L. A decrease in the daily production of saliva below 500 mL/day is termed hyposecretion or hyposialia.[7] Sialorrhea, hypersialia, hypersalivation, and ptyalism are terms used to describe salivary flow above the limits of the normal.[8]

Saliva plays a central role in oral health monitoring, regulating and maintaining the integrity of the oral hard and soft tissues.[1] It lubricates and cleans the oral cavity, possesses antibacterial, antiviral, and antifungal properties, buffers the pH, helps in chewing, speech, swallowing, and digestion, promotes taste, and contributes to the maintenance and remineralization of teeth.[9] Moreover, it may be useful in the diagnosis of various diseases.[10] The characterization by proteomic approaches—of more than 1000 salivary proteins and peptides—has allowed the identification of new salivary markers in oncology, salivary gland dysfunction, Sjögren's syndrome, systemic sclerosis, psychiatric and neurological diseases, and dental and periodontal pathology.[11–13]

1.2 INFECTION TRANSMISSION BY SALIVA AND KISSING

The infectivity of microorganisms can depend on the infective load, virulence, with some, such as the notorious *norovirus*, being extremely contagious and able to survive weeks on surfaces and fomites.[14] The detection and continuous shedding of infectious agents in saliva does not necessarily mean transmission by this route. Factors including the microorganism load, the existence of specific receptors on oral

epithelial cells, and host defenses may play an important defensive role.[15] Moreover, blood contamination in saliva—often invisible to the eye—is not uncommon mainly among active smokers[16] and individuals with poor oral health status, those with gingivitis or periodontitis,[17] and those with certain infectious diseases including human immunodeficiency virus (HIV) infection.[18]

Saliva contact can cause overt concern when using utensils such as cutlery or oral health devices, or if kissing a person with an infectious disease. However, the apparent absence of obvious disease does not guarantee the absence of infection or infective agents in saliva (or other body fluids): many diseases (especially viral) can be incubating or be subclinical (causing no or nonspecific symptoms or signs). Intimate mucosal contacts, particularly where there are epithelial breaches or substances that may impede salivary defenses (e.g., other body fluids), predispose to infection transmission.

Kissing is not exclusive to humans or primates, though it may have different connotations in different species.[19] Theories to explain kissing behavior consider it to have an origin in social and sexual interactions, premastication of foods for newborns or even the intentional transfer of microorganisms to promote immunity.[20] Kissing is seen in most human cultures,[20] and often is part of daily behavior, playing important roles in building and maintaining interpersonal relationships[21,22] and in partner selection.[23] There are, however, huge intercultural differences related to kissing; this being considered an acceptable behavior in some cultures but totally offensive in others. For example, social kissing is an accepted form of salutation in the Mediterranean and Latin cultures, in Muslim-majority societies governed by religious law there are strict taboos about whom one can kiss, or people from some areas in Sudan refuse to kiss because they fear having their soul stolen through kissing.[24] In general, kissing is considered by many of the public to have few or no serious health implications.

Different types of kissing are evident and the type of kissing may well be relevant with respect to the transmission of microorganisms, as it not only determines the capacity of the kiss to spread infectious diseases,[25] but it can also have a bearing on the chemoprophylaxis strategy to be used in "kissing contacts" in certain situations (e.g., during an outbreak of meningococcal disease).[26]

"Air kissing" is a cheek-to-cheek approximation; "osculum" is when the lips make contact with the body, usually the cheeks; "basium kiss" consists of mutual approximation of the lips with the mouth closed, exercising light pressure; and finally, there is the "saviolum kiss" in which, in addition to lip contact, the tongue is inserted into the opposite person's mouth ("French kissing," "passionate kissing," deep kissing," "active kissing," or "intimate kissing").[27] Finally "kiss of life" refers to direct, intense, and recurrent lip contact during mouth-to-mouth resuscitation—the therapy of choice for cardiorespiratory arrest in the community.

Couples may exchange an average of 5 mL of saliva during active kissing,[28] making this an activity that could favor the transmission of infectious diseases. Evidence for person-to-person transmission by kissing is limited to a few microorganisms and even this evidence can be often based on only weak scientific evidence. Published studies are heterogeneous, from isolated case reports of kissing as a "possible" cause of transmission of diseases (e.g., HIV infection)[29] to studies analyzing the inhibitory activity of the saliva on specific microorganisms (e.g., *herpes simplex*).[30] Few studies have been designed specifically to demonstrate the degree of infectivity if any of kissing, but one study showed it does not efficiently spread common cold infection by *Rhinoviruses*.[31]

Studies on the risks from mouth-to-mouth ventilation without barrier devices[32] demonstrated isolated cases of transmission of tuberculosis,[33] *herpes simplex* infection,[34] shigellosis,[35] salmonellosis,[36] and meningococcal infection.[37]

Despite this, evidence for infection transmission by kissing is not strong, so this does not justify philemaphobia (morbid fear of kissing). Paradoxically, it has even been suggested that kissing could be an evolutionary adaptation to protect against some neonatal infections (e.g., *cytomegalovirus*).[38] In reality, saliva may also have a protective role, and many animals, even humans, instinctively lick wounds—an act that may be defensive—possibly via histatins mainly.[39,40] Saliva also contains an array of factors which facilitate protection (Table 1.1).

1.3 THE PROTECTIVE ROLE OF SALIVA

Adequate salivary flow has a cleansing action and saliva also contains potentially protective constituents (Table 1.1).[40–42] Antimicrobial

Table 1.1 Antimicrobial Factors in Saliva

Factor	Antibacterial	Antiviral	Main details
Agglutinins	+	+	gp340, DMBT1 (deleted in malignant brain tumors 1)
Antibodies	+	+	sIgA (secretory Immunoglobulin A)
Calgranulin or calprotectin	+	−	Calgranulin A/B is antimicrobial by binding calcium and other metals
Cathelcidin	+	+	Cathelcidin is cleaved into the antimicrobial peptide LL-37 by both kallikrein 5 and kallikrein 7 serine proteases
Cystatin	+	+	A cysteine proteinase inhibitor which can be antiviral
Defensins	+	+	HNPs (Human Neutrophil Peptides) α,β
Histatins	+	−	A family of histidine-rich antimicrobial proteins, especially antifungal
Lactoferrin	+	+	An iron-binding glycoprotein in saliva and various other secretory fluids
Lysozyme (muraminidase)	+	−	Damages bacterial cell walls
Mucins	+	+	Glycoconjugates (glycosylated proteins) produced by epithelia. Membrane-associated mucins may also act as cell surface receptors for pathogens
Peroxidase	+	+	Produced mainly by parotid gland
Secretory leukocyte protease inhibitor	+	+	SLPI is found in saliva and many other secretions, protects epithelial tissues from serine proteases, and is antimicrobial

proteins can arise from epithelial cells, innate immune, and other cells and can modulate the microbial flora in the mouth. For example, viruses such as *noroviruses* are affected by host genetic factors [43] including histoblood group antigens (HBGAs) (i.e., the ABO blood group, the Lewis phenotype, and the secretor status).

Salivary proteins which can be protective at least against certain agents, include scavenger receptor cysteine-rich glycoprotein 340 (salivary gp-340), mucins, histatins, and human neutrophil defensins. The protein gp340—formerly salivary agglutinin—aggregates a variety of bacteria and can function as a specific inhibitor of HIV-1 and influenza A.[41] Salivary mucins MUC5B and MUC7 reduce the attachment and biofilm formation of *Streptococcus mutans* by keeping bacteria in the planktonic state.[44] Several studies have shown that salivary mucins induce phenotypic changes in *Candida albicans* at the level of mRNA transcription, which downregulate genes necessary for hyphal development and some virulence factors.[45] Saliva also contains an array of other protective proteins including tissue factor, growth factors—

especially Secretory Leukocyte Protease Inhibitor (SLPI) and Epidermal Growth Factor—which may in addition, facilitate wound healing.[39]

It has been reported that saliva inhibits oral transmission of HIV through kissing, dental treatment, biting, and aerosolization; both crude saliva and mucins MUC5B and MUC7 inhibit HIV-1 activity, probably because they trap or aggregate the virus and prevent its entry into host cells.[46] SLPI is also important. *Hantaviruses* are also sensitive to the antiviral actions of mucins,[47] and sialic acid type molecules have high activity against *human influenza viruses.*[48]

Histatins provide the first line of defense against *C. albicans*[49] and other fungi.[50] Cystatin may inhibit *coronaviruses*.[51] Moreover, saliva mediates antibody-dependent cell-mediated cytotoxicity as in HIV-1-infected individuals[52] and can regulate specific humoral defense mechanisms against microorganisms including *Cryptococcus neoformans*[53] or *Paracoccidioides*.[54]

Oral carriage of microorganisms and infections are more likely where there is hyposalivation and/or immunoincompetence—and so infections may be more prevalent in neonates who lack acquired immunity, or where immunity wanes such as in older or patients with immunocompromising conditions (e.g., malignant disease and its treatment, HIV/AIDS, or corticosteroid therapy)—particularly where the load of infecting agents is high or the microbe is virulent.

- *Specific saliva protection against oral bacteria*
  Saliva has a mechanical flushing action and there are innate immune defenses and complex interactions with microorganisms.[55,56] For example, the gene DMBT1 (Deleted in Malignant Brain Tumor 1) encodes antimicrobial proteins involved in mucosal innate immunity, and salivary DMBT1 glycoprotein (gp340) and salivary agglutinin (DMBT1(SAG)) glycoproteins which are identical, agglutinate *S. mutans* and some other Gram-positive bacteria, as well as several Gram-negative bacteria.[57] Some of the salivary components can change with disease; e.g., higher interleukin (IL)-6/IL-1β, secretory IgA, and lower lysozyme, and histatins 1 and 5 have been found in hepatic cirrhosis.[58]
  The innate and acquired immune defenses in saliva persist even after removal of lymphoid tissue in tonsillectomy: serum-derived

antimicrobial proteins (myeloperoxidase, lactoferrin, IgG) remain in high concentrations in whole saliva with no effect on the numbers of oral cariogenic *S. mutans* or on the total aerobic flora.[59]

- *Specific saliva protection against bacteria such as Pseudomonas aeruginosa*

  Pseudomonas aeruginosa often colonizes the airways in cystic fibrosis. *P. aeruginosa* binds to oral and bronchial epithelial cells,[60,61] by pili and fimbriae which promote adherence to glycosphingolipid adhesins asialo-GM1 on surfaces of host epithelia and phagocytes such as polymorphonuclear leukocytes.[62–64] Failure to isolate pathogenic organisms consistently from the upper airways in all patients with positive sputum argues against a local epithelial factor predisposing to bacterial colonization[65] and also suggests that defensive processes are in play. *P. aeruginosa* are aggregated by saliva.

  The sero-mucous products of the submandibular gland have a greater role than the serous secretions of the parotids and are possibly responsible for the differences in oral colonization by *P. aeruginosa* in different subjects.[66] The low-molecular-weight mucin (MG2) of human submandibular–sublingual saliva, and neutral cystatin, bind to pili.[67] *P. aeruginosa* interactions with *S. aureus* may be predicated on the formation of MG2–secretory IgA antibody complex, which may facilitate clearance from the oral cavity.[68]

  Interbacterial adherence between strains of *P. aeruginosa* with oral *Actinomyces viscosus* indigenous to the human mouth and with strains of *Streptococcus pyogenes*, and *Streptococcus agalactiae*, appear to involve galactosyl-binding adhesins.[69] Most oral *viridans streptococci* have potentially bacteriocin-like activity against *P. aeruginosa*.[70]

- *Specific saliva protection against viruses such as HIV*

  Saliva may also be inhibitory to HIV. Though complete inactivation may require 30 minutes of exposure, saliva may inhibit HIV-1.[71–76] A main protective mechanism of saliva may be the inactivation of HIV-transmitting leukocytes by the hypotonicity of saliva[77] and the oral transmission of HIV by seminal and other fluids introduced into the mouth may be due to their isotonicity overcoming the inactivation of HIV by isotonic saliva.[78] HIV transmission across mucosae involves complex mechanisms and the oral mucosal epithelia mucosa is less permissive for HIV replication than other sites (e.g., vagina/cervix and anal/rectal).[79] Innate immunity plays a role in protection.[80] Viral reception appears to involve both CD4 (Cluster of Differentiation 4) and a co-receptor—particularly CCR5

(Chemokine Receptor type 5).[81] The MHC appears to have a role in HIV-1 control, particularly the HLA Complex P5 (HCP5) and Human Leukocyte Antigen-C (HLA-C) and this may explain the occurrence of "Elite Supressor" patients.[82]

The scavenger receptor protein gp340—encoded by the DMBT1 gene—interacts with surfactant proteins (SP-D), and both gp340 and SP-D can individually and together interact and agglutinate some viruses and DMBT1(gp340) binds to a variety of other host proteins, including serum and secretory IgA, C1q, lactoferrin, MUC5B, and Trefoil Factor 2 (TFF2), all molecules involved in innate immunity and/or wound healing.[57] The protein gp340 appears to facilitate HIV transmission across genital but not oral mucosa.[83–86] Acquired immunity might confer some protection in re-exposures: immunization with an HIV peptide may produce HIV-inhibitory antibodies in saliva.[87]

Various glycoproteins may also be inhibitory to HIV. Crude saliva and salivary mucins MUC5B and MUC7 (both from HIV-positive people and uninfected controls) can inhibit HIV-1.[46,88] Other glycoproteins may also be implicated.[89,90]

SLPI may have an important HIV-inhibitory role,[91,92] as might human β-defensins (hBDs) from the epithelium.[93,94] Saliva may also mediate antibody-dependent cytotoxicity against HIV.[52]

- *Specific saliva protection against influenza A virus*

  Other viruses as. e.g., H5N1 *influenza virus* are particularly susceptible to human saliva, which may play a role in its infectivity and transmissibility.[48]

  Many salivary antibacterial proteins have antiviral activity, typically against specific pathogens.[41] Antiviral activities of saliva against influenza A virus (IAV) and HIV differ both in terms of specific glandular secretions and the inhibitory proteins. Whole saliva or parotid or submandibular/sublingual secretions from healthy donors inhibits IAV, whereas only submandibular/sublingual secretions are inhibitory to HIV. Among salivary proteins, scavenger receptor cysteine-rich glycoprotein 340 (gp340), MUC5B, histatins, and human neutrophil defensins at concentrations present in whole saliva inhibit IAV, while acidic proline-rich proteins and amylase have no activity nor do several less abundant salivary proteins (e.g., thrombospondin or serum SLPI).[95]

  gp340 interacts with surfactant proteins A and D (SP-D) and can interact and agglutinate IVA virus and also binds to proteins

involved in innate immunity and/or wound healing, including serum and secretory IgA, C1q, lactoferrin, MUC5B and TFF2.[57] Salivary gp340 can antagonize SP-D antiviral activities—which may be relevant to the effects of aspiration of oral contents on SP-D-mediated lung functions.[96]

Other components responsible for antiviral activity on *influenza virus*, in particular *swine origin influenza A virus* (S-OIV), include an α-2-macroglobulin (A2M) and an A2M-like protein.[97]

Salivary glycoproteins which have significant roles against IVA also include lectins (e.g., MAL-II and SNA).[98]

MUC5B inhibits IAV by presenting a sialic acid ligand for the viral hemagglutinin.[95] Other sialic acid−containing molecules may be effective against *human influenza viruses* more so than against H5N1.[48]

- *Specific saliva protection against fungi such as Candida* spp.

Both innate immunity and cell-mediated immune response are involved in defenses against fungal infections. Saliva has a mechanical defense action and components including secretory immunoglobulin A, lactoferrin, and polymorphonuclear leukocyte (PMNL) superoxide are protective.[99] A low, stimulated salivary flow rate—not a low, unstimulated flow rate—is associated with *Candida* spp. carriage.[100]

Salivary components mediate microbial attachment to oral surfaces and interact with planktonic microbial surfaces to facilitate agglutination often mediated by lectin-like proteins that bind to glycan motifs on salivary glycoproteins and help eliminate pathogens. Antimicrobial peptides in saliva appear to play a crucial role in the regulation of oral *Candida* growth. Oral candidiasis may be associated with salivary gland hypofunction and decreases of salivary lactoferrin, secretory immunoglobulin A, β-defensin 1, and β-defensin 2 antibacterial proteins.[101]

Histatins are basic histidine-rich cationic proteins present in saliva that provide the first line of defense against oral candidiasis—an important antimicrobial is histatin 5 (Hst 5),[102,103] which shows potent and selective antifungal activity and with the carrier molecule spermidine which, by binding to fungal cell wall proteins (Ssa1/2) and glycans, significantly enhances *C. albicans* killing.[49] Histatins effectively kill *C. albicans, C. glabrata,* and *C. Krusei*, and histatin 3 acts against *C. dubliniensis*.[104]

Other antimicrobial proteins include calprotectin,[105] cystatin SA1,[106] and β-defensin 2,[107] deficiencies of which predispose to chronic candidiasis. Salivary lysozyme can also be protective.[108]

The development of candidiasis in HIV-infected patients could be a consequence of inefficient lysozyme and lactoferrin concentrations and of decreased cooperation between innate and adaptive immune systems.[109] The vast majority of *Candida* isolates appear to succumb to nonspecific host immune mediators[110] but innate immunity alone is unable to stop yeast expansion in HIV-infected patients.[111]

C. albicans-secreted aspartyl proteinase (SAP1-SAP8) and phospholipase B (PLB1 and PLB2) genes are expressed during both infection and carriage of *Candida* spp. The differential expression of these hydrolytic enzyme genes correlates the expression of specific *Candida* spp. virulence genes with active candidiasis and anatomical location.[112] Salivary anti-somatic, anti-SAP2, and anti-SAP6 antibodies are not efficient in limiting candidal infection[113] and although HIV-infected patients have a high mucosal response against *C. albicans* virulence antigens, such as somatic antigen, Sap1, and Sap6,[114] this is not totally protective.

Defensins such as α-defensin (Human Neutrophil Peptides, HNPs) and β-defensin-2 (hBD-2) peptides can have antifungal and cytotoxic activities.[115] Defensins that exhibit antibacterial, antifungal, and antiviral properties are a component of the innate immune response. β-defensins (hBD-1) are cationic antimicrobial peptides encoded by the DEFB1 gene expressed in oral epithelia that may have a major role in mediating and/or contributing to susceptibility to candidiasis.[116]

Nitric oxide (NO) is involved in host resistance to infection with *C. albicans* at least in animal models. IL-4 is associated with resistance to oral candidiasis and suggests that NO is involved in controlling colonization of the oral mucosal surface with *C. albicans*.[117]

Oral epithelial cells may play a role in innate resistance against candidiasis.[118] Host defenses against *C. albicans* include epithelial cell defenses and innate and specific immune mechanisms. Cell-mediated immunity by Th1-type CD4 + T-cells is important for protection against mucosal infections, and PMNLs are important for protection against systemic infections.[119] When CD8(+) T-cell migration is

inhibited by reduced tissue E-cadherin, there is susceptibility to infection which supports a role for CD8(+) T cells in host defense against oropharyngeal candidiasis.[120]

Fungal pattern recognition receptors such as C-type lectin receptors trigger protective T-helper (Th)17 responses in the oral mucosa. The Th17/IL-17 axis is vital for immunity to fungi, especially *C. albicans*. The inflammatory cytokine IL-17 induces tumor necrosis factor (TNF)-α, and interleukins IL-1β and IL-6.[121] A systemic immune response involving T-helper 1 (Th1) cells with the production of TNF-α and IFN-γ is seen in patients with oral candidiasis.[122] Th17 cells may act through IL-17, to confer defenses via neutrophils and antimicrobial factors.[123] Oral epithelial cells also are involved in local host defenses against *C. albicans* infections via IFN-γ induced IL-18.[124]

Biofilms, some 15% of which may be due to dual *Candida* spp., contribute to the pathogenesis of oral candidiasis,[125] biofilm formation of *C. albicans* appearing to be modulated by salivary and dietary factors.[126]

C. albicans hyphal wall protein 1 (Hwp1) mRNA is present in candidiasis regardless of symptoms, implicating hyphal and possibly pseudohyphal forms in mucosal carriage as well as disease.[127] Overall, Hwp1 and hyphal growth forms appear to be important factors in both benign and invasive interactions of *C. albicans* with human hosts.

1.4 PREVENTION OF TRANSMISSION OF MICROORGANISMS BY SALIVA

Transmission of infection by saliva may be prevented or minimized by avoidance of exposure, by good oral hygiene (plaque removal), and by the use of the various substances such as some mouthwashes, and probiotics that may inhibit salivary microorganisms.[128,129]

1.5 CLOSING REMARKS AND PERSPECTIVES

Bacterial pathogens have been identified in salivary samples by specific antibody reactivity, antigen detection, or via PCR, including *Escherichia coli, Mycobacterium tuberculosis, Treponema pallidum*, and a wide range of *Streptococcus* spp. More than 20 viruses have also been detected; these include a number of *Herpes viruses, Hepatitis viruses, Human Immunodeficiency Viruses, Papillomavirus, Influenza*

virus, or Poliovirus. Nonviral and nonbacterial infectious agents including fungi and protozoa are also detectable, usually by antibodies to these infectious agents. Recognition of the components of the oral microbiota can help in the prediction of the onset, progression, and prognosis of oral and systemic diseases. Tests for these pathogens are currently under development. Omics methods, such as 16S rRNA sequencing, metagenomics, and metabolomics, can play an essential role to explore microbial community and its metabolite production, without the biases of microbial culture. Saliva contains many antibacterial, antiviral, and antifungal agents which modulate the oral microbial flora. Consequently, detection and shedding of infectious agents in saliva does not necessarily mean transmission by this route. Anyway, the presence of these pathogens in saliva is particularly important in immunosuppressed patients in whom infections can result fatal. Moreover, the defensive ability of saliva against emerging infectious diseases caused by new or previously unrecognized microorganisms remains unknown.

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