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MICROBIOME DIVERSITY IN THE SALIVA RELATED ORAL AND SYSTEMIC DISEASES

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ABSTRACT: This review aimed to evaluate findings related to the human normal salivary microbiomes, the presence of opportunist salivary microbiome concerning oral and systemic diseases, and the use of salivary microbiome metagenomic analysis. **Method**: This review accomplishes using PubMed, Science Direct, and Google scholar. After reading the titles and abstracts, 2.718 works of literature screens for this review, content analysis performs. **Results**: Human normal salivary microbiomes consist of yeast, gram-positive, and gram-negative bacteria. A commensal microbial community founds in healthy people. An opportunist microbial community establishes in unhealthy people. It is essential to note an association between the opportunist microbiome composition with the personal health condition. Specific opportunist microbiome relates to particular diseases, such as diabetes, respiratory diseases, cancer, autoimmune, and viral infections. Even is different results of the conventional method and the modern methods (metagenomic analysis), both approaches can determine the presence of specific opportunist salivary microbiome concerning certain systemic diseases. **Conclusion**: Salivary microbiome composition can be a biomarker for people's health conditions and various systemic diseases. Both conventional methods and the modern method can be used complementarily for biomarker determination.

KEYWORDS: saliva, bacteria, metagenomic, microbiome, and virus

I. INTRODUCTION

Salivary microbiome composition is associated with human health or unhealthy condition (oral and systemic disease). The salivary microbiome is beneficial for medical diagnosis, because of decrease complexity and non-invasive.[1] Two community groups in saliva are recognised, i.e., the commensal or normal microbiome in the healthy people and opportunist community related to the specific disease. Various salivary microbiome patterns relate to a range of oral, systemic diseases, and viral infections. The temporal variability of the human opportunist salivary microbiome becomes essential for determining health and disorder relationships.[2] Therefore, salivary microbiome analysis may have a potential diagnostic or prognostic value related to specific conditions.[3]

This review aims to achieve the following objectives:

- to evaluate the current knowledge on the regular salivary microbiome community;
- to find a relationship between opportunist oral microbiome and the specific disease (oral, systemic diseases, and viral infection); and
- to apprehend the need and prospect of metagenomic analysis for the salivary microbiome associated diseases

For writing this review, searching was done with PubMed, Science Direct, and Google Scholar during August 2020, mainly for the last five years articles. The combined keywords were saliva, bacteria, metagenomic, microbiome, and virus. The searching result was 2.718 articles. After screening, the most relevant articles were 96 articles.

II. NORMAL SALIVARY MICROBIOME COMMUNITY

Based on the conventional methods, the microbiome profile of saliva can obtain. Microbiome traditional methods are done basically with the isolation of a single colony, purified, and biochemical characterisations. Five main genera report as normal salivary microbiome community. Streptococcus,

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Veillonella, Prevotella, Neisseria, Fusobacterium are the major genera of the normal salivary microbiome. They are reported and linked to the diverse oral health microbiome. [4]

According to Leake et al., [5] saliva contains around 500 million microbiome cells in one millilitre (mL) of saliva. Microbiome cells are aerobic and anaerobic and live in an always high temperature, humidity, and regular food arrival. Usually, the normal salivary microbiome detects as dominant or majority bacteria in healthy people rather than unhealthy people. Probably, this due to the dominant number of opportunist compared or less more competitive than the normal microbiome. [5]

Streptococcus species found in healthy people's saliva, people with oral diseases, and systemic diseases. (Table 1 and 2). Streptococcus usually divides into four groups, mutans, salivarius, angiosus, and mitis. Many of them find attached to teeth, surfaces of the oral cavity, dental plaque, and mucosal membranes. They are biofilm formed in the oral cavity. Some of them may exist as a planktonic form in saliva.

The other two members of the normal salivary microbiome are Neisseria and Veillonella. Neisseria spp., Gram-negative cocci, are facultative and anaerobic cocci. They are inhabitants of the oral cavity in low quantities. Veillonella spp., are also Gram-negative cocci, but a strict anaerobe. Another two prevalent members of the normal salivary microbiome are Prevotella and Fusobacterium that are Gram-negative bacilli and obligate anaerobe.

III. THE ASSOCIATION BETWEEN SALIVA OPPORTUNIST MICROBIOME WITH CERTAIN DISEASES (ORAL, SYSTEMIC DISEASES AND INFECTIOUS VIRUS DISEASES)

Saliva contains multiple components that can use for risk assessment of systemic disease. Microbiome and host markers in saliva are essential for identifying periodontitis, autoimmune and immunodeficiency disease, diabetes, burning mouth syndrome, cough sensitivity, and tuberculosis. Changes in the microbiota of saliva can assist us with understanding what happens when the body provokes them to another condition because of disease. [6]

The opportunist microbiome community's composition influence by the type of oral disease, namely caries, periodontal Infection, and peri-implant Infection (Table 1). The species composition is significantly varied, even mixed with the commensal community. Several members of opportunist microbiome found as specific microbiome in oral caries, periodontitis, or peri-implant infection. Caries characterised by the presence of lactic acid bacteria, such as Bifidobacterium and Lactobacillus. A mixture of gram-negative and gram-positive bacteria characterises periodontitis. Gram-negative bacteria represent the peri-implant infection, for example, Escherichia coli and Klebsiella pneumonia.

Opportunist microbiome is associated with specific systemic diseases or systemic diseases, such as diabetes, respiratory Infection, AIDS. The salivary yeast opportunist population, mainly Candida albicans, is found only in the saliva of patients with diabetes and respiratory infection. Both gram-positive and negative-gram salivary bacteria find in diabetes, respiratory infection, skin infection, AIDS, local and systemic, and cystic fibrosis, but not in the rest of the diseases. The opportunist microbiome in the saliva of patients with diabetes and respiratory infection is more diverse than the other condition, probably due to the available nutrient, such as glucose, and the short distance between the disease (respiratory tract) and mouth (saliva).

The salivary microbiome is a complex microbiome ecosystem consisting of yeast bacteria and viruses associated with many metabolic functions. Changes in the salivary microbiome composition can lead to several diseases, including metabolic disorders. However, the presence of an opportunist microbiome may indicate the existence of a specific illness. Microbiome flora members can become a pathogenic agent and harmful bacteria. Numerous research displays a direct link between variations of bacterial, fungi, and viruses associated disorder. The microbiome community may go through a move in composition, and bacteria related to disorder can progress to a dominant part of the community. [6]

Composition range of microbiome occur for various factors but at least in part as a reaction to changes in the host environment, such as the rise of oral or systemic diseases. This change in proportions of the microbiome may allow sometime specific opportunist microbiome to become principal and acts as a biomarker of systemic diseases. [6] Saliva microbiome analysis is promoted as a way to detect oral and systemic disease. The presence of an opportunist microbiome needs to be managed with appropriate antimicrobial agents to maintain a healthy oral cavity.

In the next following sessions, the salivary microbiome association discusses two categories: diseases, oral diseases, and systemic diseases. The salivary microbiome influences an oral biofilm of shedding (epithelial) and non-shedding (tooth) surfaces. [7]

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3.1. Association of the salivary microbiome with oral diseases

The salivary microbiome species can distinguish individuals with oral disease (caries, periodontal disease, and peri-implant infection) from healthy individuals. There are specific opportunist species related to the type of oral disease (Table 1). The species composition is significantly different. Members' normal salivary microbiome finds in oral caries and infection. Interestingly, the average oral microbiome's presence is specific according to the type of oral disease. This probably due to the different microenvironments of the disease.

Certain salivary microbiome features may help in identifying periodontitis individuals. Porphyromonas gingivalis is the major pathogen associated with it. The presence of this organism is high correlates with preterm and low birth weight babies. P.gingivalis vertically transmitted from mother to child.[8]

Yeast, such as Candida species is involved in several oral diseases and has been identified in numerous oral cavity sites. The sites from which Candida albicans isolates include caries, biofilm formation, oral carcinogenesis, periodontal. Moreover, Candida dubliniensis associates with caries. [9]

Several members of gram-positive bacteria of the saliva microbiome are related to oral disease. Streptococcus mutans and Lactobacillus species are most commonly associated with caries. [10] [11] Other gram-positive bacteria, such as Actinomyces dentalis, Aggregatibacter actinomycetemcomitans, Bacillus subtilis, Corynebacterium argentoratense, Staphylococcus aureus have been reported to cause periodontitis. [12] [13]

Members of Gram-Negative Bacteria are considered to be involved with periodontal diseases. According to their association with periodontal disease, Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia as "red complex" species are classified as the most described. Other biofilm species associated with periodontal disease are Capnocytophaga leadbetteri, Corynebacterium matruchotii, Bacteroides, Proteobacteria, Treponema parvum, Neisseria elongata, Veillonella, Pigmentiphaga, and Fusobacterium.[14] [15-17]

3.2. The association of salivary microbiome with the systemic diseases

Candida albicans also showed a relationship not only with oral disease but also with systemic diseases. The specific salivary opportunist species are associated with specific systemic diseases, such as diabetes, respiratory Infection, AIDS. Both gram-positive and negative saliva microbiome founds in diabetes, respiratory infection, skin infection, AIDS, local and systemic, and cystic fibrosis, but not in the rest of the diseases. The opportunist microbiome in the saliva of patients with diabetes and respiratory infection is more diverse than the other disease. The opportunist bacteria is probably due to the available nutrient, such as glucose, and the short distance between the infection (respiratory tract) and mouth (saliva). Studies on Candida albicans and Candida tropicalis suggest that a significant impact happens on respiration disease's clinical outcome, such as bronchial asthma and related to smokers. [18] [19] Candida colonisation correlates with an increased risk of diabetes mellitus. [20] [21]

Salivary opportunist yeast, mainly Candida albicans, is found only in the saliva of patients with diabetes and respiratory infection. Diabetes mellitus is also associated with oral microbiome infection, of which Actinomycetes and Streptococcus are causative agents. [17] [21] Greater diversity and quantity of yeasts of the genus Candida finds in patients with decompensated DM2. Few studies have also reported the microbiome composition in diabetes and health using saliva levels of oral Candida albicans and Streptococcus mutans. The salivary microbiome in patients with diabetes differs from that in healthy control. [22]

Like pneumonia and respiratory diseases often find by gram-negative bacteria, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli that did not find in healthy mouths. Combined bacterial levels are associated with pneumonia. [23] But other factors may influence the presence of these opportunist bacteria, such as recovery from stroke, age, and gender. [24]

Salivary microbiome composition associates with various general health conditions. Studies show that Streptococcus implicates in infections in patients with immunodeficiency (autoimmune) and liver abscesses. [3] Autoimmune polyendocrine syndrome type-1 (APS-1) is caused by mutations in the Autoimmune Regulator gene. Increasing evidence shows a capability function of the salivary microbiome in the pathologic process of autoimmunity. [12] In the case of Primary sicca syndrome, and excessive microbial range may detect in the Primary Sicca Syndrome, with bacteroidetes, firmicutes, and proteobacteria. [25] Autoimmune hepatitis in Veillonella shows massive growth in oral compared to healthy control with a concurrent reduction in Streptococcus. Billiary cholangitis confirmed that Eubacterium and Veillonella were substantially enhanced and fusobacterium was generally declining in the oral compared to hepatocellular carcinoma. [26] The relative abundance of Veillonella correlates with immunoglobulin A, immunoglobulin 8, and immunoglobulin 1β within saliva. [26]

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Enterococcus faecalis associated with bacteremia, systemic and local infections.[27] The opportunistic pathogen, such as Staphylococcus hominis reported, can cause bloodstream infections. [27] In the salivary microbiome, patients with previous Hepatic Encephalopathy have a decreased relative abundance of the normal microbiome, whereas potentially pathogenic ones (Enterobacteriaceae, Enterococcaceae) are increasing. [28] However, the close lot of Lactobacillaceae in the saliva was higher in minimal hepatic encephalopathy (MHE), whereas autochthonous Lachnospiraceae were higher in those without MHE. [29]

Short-term hospitalisation and the use of antibiotics influence the salivary microbiome composition. The pathogenic Enterobacteriaceae persist much longer in hospital infected with oral fluids, in particular drains, and sinks, which can be well- installed assets of outbreaks of drug-resistant Enterobacteriaceae. Usage of antibiotics changes the variety and species composition of the salivary microbiome. In the case of amoxicillin, more significant reductions in variety have happened. Most often prescribed antibiotics can bring about sustained reductions in microbiota diversity, which can have implications for maintaining human health and disease.[30]

3.3. Association of infectious virus diseases and opportunist salivary microbiome

Viruses are crucial members of the salivary microbiome. Alterations to the salivary microbiome can bring about in human disease, host resilience to pathogens also decreases. The human salivary virus lists in Table 3. They can be divide into two groups, gland salivary virus and the non-gland salivary virus. Viruses in the latter group find in blood, skin, liver, and other organs. Several viruses found in the oral fissure are Epstein-Barr virus, HIV, hepatitis C virus, herpes simplex viruses, human papillomavirus, norovirus, and rabies. They are also often the presence in saliva and followed with the company of an opportunist microbiome.

IV. METAGENOMIC ANALYSIS FOR THE IDENTIFICATION OF BIOMARKER MICROBIOMES IN SALIVA

Metagenomic analysis of the salivary microbiome can carry with the omics or sequencing technology. Conventional identification methods are still widely used until today, and even they have three significant limitations. Firstly, it refers only to the in vitro cultivable microbiome. Secondly, some strains have exceptional biochemical features that do not fit the sequence of genus and species. Thirdly, they are time-consuming. Fortunately, there are many new approaches available now that are not reliant on live cultures. They can simultaneously analyse the salivary community members and sometimes show minute variations between microbiomes that avoid conventional means of detection.

Modern Methods for identifying bacteria include Microarray-Based Identification, Immunological (ELISA), Chemical Analytic (Fatty Acid Profiling, Metabolic Profiles /Chemo-Profiling), and PCR-Based Identification. Only Real-Time PCR addressed in this session due to the most frequently used molecular identification for the microbiome. One can easily diagnose and identify microbiome directly from clinical samples using PCR, therefore improving the diagnostic procedures.

The 16S rRNA gene for bacterial PCR recognition is the gold standard sequence, whereas the Internal Transcribed Spacer is the critical identifier for fungal forms of barcodes. Bacterial in saliva samples of T2DM was much higher than in the healthy non-diabetic controls using 16S rRNA gene sequencing. [22] Streptococcus is the predominant genera encountered among healthy controls. [8] In the case of periodontitis, Treponema sp, TM7 sp, Prevotella sp, and Capnocytophaga leadbetter reported using 16S rRNA sequencing.[31]

Bacterial 16S rRNA sequencing is a community-wide culture-free approach that pushes the study of microbial diversity associated with humans, including the salivary microbiome. The Ion Torrent Personal Genome Machine is one of the latest methods available. Ion Torrent may analyse the profile of the human saliva microbiome.[32]

4.1. Metagenomics analysis of the normal salivary microbiome

Metagenomic analysis of saliva samples can conduct to get a comprehensive profile of the microbiome community. At once time analysis, microbiome metagenomic analysis can detect the genus Bifidobacterium, Prevotella, Capnocytophaga, Leptotrichia, Neisseria, and Streptococcus. Proteobacteria, [33] In another case, the use of 16S rRNA sequence shows microbiome community diversity around 40 microbiome genera described in the human oral cavity.[34] Compared with the result of the conventional method, the metagenomic analysis can give more information. The identified members of the normal salivary microbiome, Streptococcus, Prevotella, and Neisseria, can be detected by metagenomic analyses. Nevertheless, Fusobacterium and Veillonella are not detected by the metagenomic analysis. Besides that, the metagenomic research shows

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additional familiar members of the salivary microbiome, such as Bifidobacterium, Capnocytophaga, Leptotrichia, and Proteobacteria.

4.2. Metagenomic analysis of the opportunist salivary microbiome

4.2.1. Metagenomic study of oral disease

One of the advantages of using metagenomic analysis is its ability to help us to detect prevailing conditions at an early stage, such as caries and periodontitis often diagnosed at late stages of the disease. Saliva is a right candidate biomarker associated with oral health and diseases. Caries and periodontitis are associated with the presence of various pathogens, such as Porphyromonas gingivalis and Streptococcus. [35]

The use of metagenomic analysis results in hundreds of identified bacterial species. The majority of bacterial species (around 85%) shared between samples from orally healthy people, dental carriers, and periodontitis patients. The rest is associated with periodontitis, caries, or oral health people.[36] Based on the metagenomic analysis, conventional pathogens such as Porphyromonas gingivalis, Parvimonas Micra, and Tannerella forsythia, as well as cariogenic bacteria like Streptococcus mutans and Lactobacillus species identified with significantly higher relative abundance in samples of patients with caries and periodontitis. [35]

4.2.2. Metagenomic analysis of systemic diseases

The advent of metagenomic analysis facilitates an 'open-ended' understanding of and interplay with the health of the human microbiome community. Currently, there is proof that salivary microbiome patterns linked to a variety of autoimmune, metabolic, and similar immunodeficiency conditions. Evolving signs of association with systemic diseases demonstrate prognostic and diagnostic significance for saliva microbiome research. [3]

Beside diagnosis with the conventional methods, the saliva (sputum and mucus) can be analysed metagenomically to detect the biofilm-forming Pseudomonas aeruginosa. Some biofilm-forming bacteria, such as Achromobacter xylosoxidans, Burkholderia multivorans, Mycobacterium abscessus, and Stenotrophomonas found in chronic biofilm infections caused by cystic fibrosis. [37]

Metagenomic analysis can provide information about the dental plaque that functions as a source of respiratory pathogens that can lead to biofilms in the lungs and the endotracheal tube (ETT). The metagenomics analysis of mechanically ventilated patients can classify the ETTs, dental plaque, and non-directed bronchial lavages (NBLs). Detected microbiome are primarily salivary species, along with Fusobacterium nucleatum, Streptococcus salivarius, and Prevotella melaninogenica with respiratory pathogens which includes Haemophilus influenza, Pseudomonas aeruginosa, Staphylococcus aureus, and Streptococcus pneumoniae. The close association between the microbiomes of dental plaque, ETTs, and NBLs indicate that the oral fissure is also a significant location involved in microbiome aspiration to the lower airway and ETT. [38]

Metagenomic sequencing analysis of salivary samples from individuals with rheumatoid arthritis (RA) shows dysbiosis. Dysbiosis detected in the salivary microbiome of RA patients. Change in the saliva microbiome distinguishes people with RA from healthy people. In particular, Haemophilus spp. are depleted in individuals with RA and negatively correlate with serum autoantibodies. In contrast, Lactobacillus salivarius is over-represented in individuals with RA and is present in increased amounts in cases of very active RA. Relevant improvements in the salivary microbiome in people with RA and examples on alternative ways to use microbiome structure for prognosis and diagnosis. [39]

The salivary microbiome correlates with inflammation in cirrhosis cases. A relative abundance of the commensal microbiome is reduced in hepatic encephalopathy while potentially Enterobacteriaceae are increased in saliva. The cirrhotic saliva microbiome demonstrates a correlation with systemic inflammation. Dysbiosis is represented by a reduction in commensal bacteria and found in the saliva of patients with cirrhosis. Patients with cirrhosis impair salivary defences and worse inflammation. These findings can represent a global change in cirrhosis between the mucosal and immune interfaces.[40]

4.3. Salivary viral metagenomics

The metagenomic approaches for viral communities show that probably 50% of viral sequences are "unknown." The remaining 50% "known" sequences have low amino acid similarities to the known viral proteins and thus represent an uncategorised group. [41]. The current conventional diagnosis method relies on antibody protein-protein interaction. There is no possibility of a culture virus-like bacterial culture. Therefore, the metagenomic method is significant for the rapid detection of viral infection even at the early stage of disease or for virus carriers. The metagenomic analysis can also analyse the salivary viral community, not only just for a single viral type.

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The modern method of metagenomics can be used with PCR or RT PCR. With this method, analysis can be done only for a single type of virus. For example the saliva sample diagnosis of

- Human congential cytomegalovirus (HCMV) [42] [43] [44] [45] [46] [47]
- Zika virus (ZIKV) [48] [49]
- Dengue virus (DENV) [50]
- Human polyomaviruses (HPyVs) HPyV (HPyV1-HPyV4 [former BKPyV, JCPyV, KIPyV, and WUPyV, respectively]) The distribution of viral species varies considerably between regions as well as within regions.[51]
- Coxsackieviruses B (CV-B) There is an anti-CV-B4 activity in the saliva of patients with type 1 diabetes that may be a useful marker to study the role of CV-B in the pathogenesis of the disease.[52]
- DNAs of human herpesviruses-6 (HHV-6) and -7 (HHV-7) [53]
- Rotaviruses [54]

The metagenomic analysis using various types of next-generation sequencing may analyse the presence of several viruses simultaneously. So far, there is a limited report available for the simultaneous metagenomics analysis for the salivary virus. But there are cases that no saliva-based reported as follows

- The excellent specifity of metagenomic with next-generation sequences is a critical tool for detecting human viruses. The viral composition can be accomplished in the oral setting by next-generation sequence and genomic details of human saliva on DNA and RNA viral populations. [55]
- A research report on the bat's metagenomic analysis can be plied for the human sample, even not a human case. The metagenomic study of bat encompasses can recognise viral population diversity. A metagenomic approach identifies thousands of viral sequences in the saliva of the bat. [56] These findings provide significant insight that a similar study can be applied to human salivary viruses.

Pathogenic viruses can replicate, invade, and can cause disease inside the human cells. Continued production and reappearance of pathogenic viruses have become a problem for public health. Rapid detection is crucial to implement specific control measures and restrictions on the spread of the virus. [57] Metagenomic analysis can be applied to clinical saliva samples as a non-targeted diagnostic and surveillance tool. This approach is precious since the virus is not easily cultivated and detected. The metagenomic analysis also provides invaluable insights into the virus-host interactions, epidemiology, ecology, and evolution of viruses. [58] Molecular biology and fundamental principles of molecular technologies commonly used to identify and characterise pathogenic viruses. [57] Bioinformatic support for managing a comprehensive database for virome should develop as well.

V. CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

This review is an attempt to associate the human salivary microbiome with oral and systemic diseases. Their shifts may give valuable information to us. According to the objectives of this review, three highlights of the conclusion formulated as follows:

- The human normal salivary microbiome is a unique and poly species community. They present in the saliva of healthy people, and not always in people with oral or systemic disease.
- Salivary opportunist microbiome is associated with specific diseases, mainly to oral diseases like caries, periodontal disease, and peri-implant disease. In many cases, they related to systemic diseases, primarily diabetes, and respiratory diseases. Certain virus pathogenicity can be detected in saliva.
- The metagenomic analysis is a useful and rapid modern method in determining the uncultured microbiome. The detail and comprehensive profile of the salivary microbiome composition can be recognised. This method can give information on the healthy condition of the people and transmission infectious agents and biomarkers of non-communicable diseases.

Recommendations

Based on the findings obtained from this reviewing process, three recommendations are suggested.

- The research on the human normal salivary microbiome should further investigated using modern metagenomics tools. Their presence is specific for healthy people and becomes a promising biomarker for healthy or unhealthy conditions.

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- The studies on the opportunist salivary microbiome related to oral or systemic diseases are essential for two aspects. Firstly, they are useful for the early detection of diseases. Secondly, they can help in developing a therapeutic strategy for the oral health cavity.
- Microbiome profiles generated by 'omics' approaches used extensively to explore the co-occurrence and co-exclusion patterns in saliva communities. When use of metagenomic salivary analysis is possible for the salivary microbiome community, then the microbiome profile may give specific and accurate information to predict the healthy condition and develop a therapy strategy for the oral cavity.

Conflict of interest: none

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VI. REFERENCES

[1]. Cabral, D.J. et al., The salivary microbiome is consistent between subjects and resistant to impacts of short-term hospitalisation. Sci Rep, 2017. **7**(1): p. 11040.
[2]. Cameron, S.J., et al., The human salivary microbiome exhibits temporal stability in bacterial diversity. FEMS Microbiol Ecol, 2015. **91**(9): p. fiv091.
[3]. Acharya, A., et al., Salivary microbiome in non-oral disease: A summary of evidence and commentary. Arch Oral Biol, 2017. **83**: p. 169-173.
[4]. Murugesan Selvasankar , SFAA, Parul Singh , Marwa Saadaoui , Manoj Kumar and Souhaila Al Khodor, Profling the Salivary microbiome of the Qatari population. Journal of Translational Medicine, 2020. **18**(127).
[5]. Leake, S.L., et al., The salivary microbiome for differentiating individuals: proof of principle. Microbes Infect, 2016. **18**(6): p. 399-405.
[6]. Tribble, K.J.E.a.G.D., Salivary Diagnostics and the Oral Microbiome Charles F. Streckfus (Ed.) Advances in Salivary Diagnostics 2015. **Springer** p. 83-119.
[7]. Gazdeck, R.K., et al., diversity of the oral microbiome between dentate and edentulous individuals. Oral Dis, 2019. **25**(3): p. 911-918.
[8]. Adhikari, K., C.S. Saimbi, and B.P. Gupta, Estimation of Transmission of Porphyromonas Gingivalis from Mother to Child through Saliva. JNMA J Nepal Med Assoc, 2018. **56**(212): p. 781-786.
[9]. Al-Ahmad, A., et al., Prevalence of Candida albicans and Candida dubliniensis in caries-free and caries-active children in relation to the oral microbiota-a clinical study. Clin Oral Investig, 2016. **20**(8): p. 1963-1971.
[10]. Bachtiar, E.W. and B.M. Bachtiar, Relationship between Candida albicans and Streptococcus mutans in early childhood caries, evaluated by quantitative PCR. F1000Res, 2018. **7**: p. 1645.
[11]. Ademe, D., D. Admassu, and S. Balakrishnan, Analysis of salivary level Lactobacillus spp. and associated factors as determinants of dental caries amongst primary school children in Harar town, eastern Ethiopia. BMC Pediatr, 2020. **20**(1): p. 18.
[12]. Alves, L.A., et al., identification of microbiomes in biofluids of individuals with periodontitis and chronic kidney disease using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry. Rapid Commun Mass Spectrom, 2016. **30**(10): p. 1228-1232.
[13]. Arivaradarajan, P., et al., identification of an antibacterial protein by functional screening of a human oral metagenomic library. FEMS Microbiol Lett, 2015. **362**(18): p. fnv142.
[14]. Acharya, A., et al., Species-Level Salivary Microbial Indicators of Well-Resolved Periodontitis: A Preliminary Investigation. Front Cell Infect Microbiol, 2019. **9**: p. 347.
[15]. Zhang, F., et al., Exploring salivary microbiota in AIDS patients with different periodontal statuses using 454 GS-FLX Titanium pyrosequencing. Front Cell Infect Microbiol, 2015. **5**: p. 55.
[16]. Zhou, S., et al., Oral microbial flora of patients with Sicca syndrome. Mol Med Rep, 2018. **18**(6): p. 4895-4903.
[17]. Anbalagan, R., et al., Next generation sequencing of oral microbiota in Type 2 diabetes mellitus prior to and after neem stick usage and correlation with serum monocyte chemoattractant-1. Diabetes Res Clin Pract, 2017. **130**: p. 204-210.
[18]. Akram, Z., et al., Comparison of oral Candida carriage in waterpipe smokers, cigarette smokers, and non-smokers. J Oral Sci, 2018. **60**(1): p. 115-120.

[19]. Alka, K., et al., Estimation of salivary Candida albicans counts in asthmatic adult patients taking anti-asthmatic medication for 3-5 years. J Oral Maxillofac Pathol, 2018. **22**(3): p. 341-346.
[20]. Aitken-Saavedra, J., et al., Diversity, frequency and antifungal resistance of Candida species in patients with type 2 diabetes mellitus. Acta Odontol Scand, 2018. **76**(8): p. 580-586.
[21]. Babatzia, A., et al., Clinical and microbial oral health status in children and adolescents with type 1 diabetes mellitus. Int Dent J, 2020. **70**(2): p. 136-144.
[22]. Abdelmegid, F., et al., Effect of Honey and Green Tea Solutions on Streptococcus mutans. J Clin Pediatr Dent, 2015. **39**(5): p. 435-41.
[23]. Subramaniam, N. and A. Muthukrishnan, Oral mucositis and microbial colonisation in oral cancer patients undergoing radiotherapy and chemotherapy: A prospective analysis in a tertiary care dental hospital. J Investig Clin Dent, 2019. **10**(4): p. e12454.
[24]. Aida, K.L., et al., Influence of a preschool preventive dental programme on caries prevalence, oral care and secretory immunity to Streptococcus mutans in young adults. Int J Dent Hyg, 2018. **16**(2): p. 249-256.
[25]. Zhang, M., et al., Profiling of Oral and Nasal Microbiome in Children With Cleft Palate. Cleft Palate Craniofac J, 2016. **53**(3): p. 332-8.
[26]. Bachtiar, E.W., et al., Enterococcus faecalis with capsule polysaccharides type 2 and biofilm-forming capacity in Indonesians requiring endodontic treatment. J Investig Clin Dent, 2015. **6**(3): p. 197-205.
[27]. Zeng, Y., et al., Identification of Non- Streptococcus mutans Bacteria from Predente Infant Saliva Grown on Mitis-Salivarius-Bacitracin Agar. J Clin Pediatr Dent, 2020. **44**(1): p. 28-34.
[28]. Høiby, N., et al., diagnosis of biofilm infections in cystic fibrosis patients. Apmis, 2017. **125**(4): p. 339-343.
[29]. Emami, A., et al., Evaluating the Saliva of Burn ICU Patients for Resistant Infections Harbor Metallo-β-Lactamase Genes. J Burn Care Res, 2020. **41**(3): p. 647-651.
[30]. Abeles, S.R., et al., Microbial diversity in individuals and their household contacts following typical antibiotic courses. Microbiome, 2016. **4**(1): p. 39.
[31]. Alamoudi, NM, et al., Effect of Probiotic Lactobacillus reuteri on Salivary Cariogenic Bacterial Counts among Groups of Preschool Children in Jeddah, Saudi Arabia: A Randomised Clinical Trial. J Clin Pediatr Dent, 2018. **42**(5): p. 331-338.
[32]. Dassi, E., et al., Enhanced microbial diversity in the saliva microbiome induced by short-term probiotic intake revealed by 16S rRNA sequencing on the IonTorrent PGM platform. J Biotechnol, 2014. **190**: p. 30-9.
[33]. Yeo, L.F., et al., Health and saliva microbiomes of a semi-urbanised indigenous tribe in Peninsular Malaysia. F1000Res, 2019. **8**: p. 175.
[34]. Nasidze, I., et al., High diversity of the saliva microbiome in Batwa Pygmies. PLoS One, 2011. **6**(8): p. e23352.
[35]. Belstrøm, D., et al., Microbial profile comparisons of saliva, pooled and site-specific subgingival samples in periodontitis patients. PLoS One, 2017. **12**(8): p. e0182992.
[36]. Belstrøm, D., et al., Salivary microbiota in individuals with different levels of caries experience. J Oral Microbiol, 2017. **9**(1): p. 1270614.
[37]. Hoiby, N., et al., diagnosis of biofilm infections in cystic fibrosis patients. Apmis, 2017. **125**(4): p. 339-343.
[38]. Marino, P.J., et al., Community analysis of dental plaque and endotracheal tube biofilms from mechanically ventilated patients. J Crit Care, 2017. **39**: p. 149-155.
[39]. Zhang, X., et al., The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalised after treatment. Nat Med, 2015. **21**(8): p. 895-905.
[40]. Bajaj, J.S., et al., Salivary microbiota reflects changes in gut microbiota in cirrhosis with hepatic encephalopathy. Hepatology, 2015. **62**(4): p. 1260-71.
[41]. Sultana, G.N.H., The Use of Metagenomic Approaches to Analyse Changes in Microbial Communities. Libertas Academica freedom to research, 2013. **6**: p. 37-48.
[42]. Choudhary, A., et al., Comparison of conventional, immunological and molecular techniques for the diagnosis of symptomatic congenital human cytomegalovirus infection in neonates and infants. Indian J Med Microbiol, 2015. **33 Suppl**: p. 15-9.
[43]. Correa, C., et al., Diagnosis, gB genotype distribution and viral load of symptomatic congenitally infected CMV patients in Cuba. J Perinatol, 2016. **36**(10): p. 837-42.
[44]. Pinninti, S.G., et al., Comparison of saliva PCR assay versus rapid culture for detection of congenital cytomegalovirus infection. Pediatr Infect Dis J, 2015. **34**(5): p. 536-7.
[45]. Ross, S.A., et al., detection of congenital cytomegalovirus infection by real-time polymerase chain reaction analysis of saliva or urine specimens. J Infect Dis, 2014. **210**(9): p. 1415-8.
[46]. Ronchi, A., et al., detection of cytomegalovirus in saliva from infants undergoing sepsis evaluation in the neonatal intensive care unit: the VIRIoN-C study. J Perinat Med, 2018. **47**(1): p. 90-98.

[47]. Pitlick, M.M., et al., Determining the prevalence of cytomegalovirus infection in a cohort of preterm infants. J Neonatal Perinatal Med, 2015. **8**(2): p. 137-41.
[48]. Cordeiro, M.T., Laboratory diagnosis of Zika virus. Top Magn Reson Imaging, 2019. **28**(1): p. 15-17.
[49]. Musso, D., et al., Detection of Zika virus in saliva. J Clin Virol, 2015. **68**: p. 53-5.
[50]. Poloni, T.R., et al., High prevalence of clinically unsuspected dengue disease among children in Ribeirao Preto city, Brazil. J Med Virol, 2016. **88**(10): p. 1711-9.
[51]. Pena, G.P.A., et al., Human polyomavirus KI, WU, BK, and JC in healthy volunteers. Eur J Clin Microbiol Infect Dis, 2019. **38**(1): p. 135-139.
[52]. Badia-Boungou, F., et al., Marker of coxsackievirus-B4 Infection in saliva of patients with type 1 diabetes. Diabetes Metab Res Rev, 2017. **33**(7).
[53]. Miyazaki, Y., et al., Monitoring of human herpesviruses-6 and -7 DNA in saliva samples during the acute and convalescent phases of exanthem subitum. J Med Virol, 2017. **89**(4): p. 696-702.
[54]. Zhang, X.F., et al., P[8] and P[4] Rotavirus Infection Associated with Secretor Phenotypes Among Children in South China. Sci Rep, 2016. **6**: p. 34591.
[55]. Parras-Moltó, M. and A. López-Bueno, Methods for Enrichment and Sequencing of Oral Viral Assemblages: Saliva, Oral Mucosa, and Dental Plaque Viromes. Methods Mol Biol, 2018. **1838**: p. 143-161.
[56]. Salmier, A., et al., Virome analysis of two sympatric bat species (Desmodus rotundus and Molossus molossus) in French Guiana. PLoS One, 2017. **12**(11): p. e0186943.
[57]. Artika, I.M., A. Wiyatno, and C.N. Ma'roef, Pathogenic viruses: Molecular Detection and characterisation. Infection, Genetics and Evolution, 2020. **81**: p. 104215.
[58]. Paez-Espino, D., et al., diversity, evolution, and classification of virophages uncovered through global metagenomics. Microbiome, 2019. **7**(1): p. 157.
[59]. Arzmi, M.H., et al., Polymicrobial biofilm formation by Candida albicans, Actinomyces naeslundii, and Streptococcus mutans is Candida albicans strain and medium dependent. Med Mycol, 2016. **54**(8): p. 856-64.
[60]. Arzmi, M.H., et al., Monospecies and polymicrobial biofilms differentially regulate the phenotype of genotype-specific oral cancer cells. Carcinogenesis, 2019. **40**(1): p. 184-193.
[61]. Akhi, R., et al., Cross-reactive saliva IgA antibodies to oxidised LDL and periodontal pathogens in humans. J Clin Periodontol, 2017. **44**(7): p. 682-691.
[62]. Alanzi, A., et al., Effect of Lactobacillus rhamnosus and Bifidobacterium lactis on gingival health, dental plaque, and periodontopathogens in adolescents: a randomised placebo-controlled clinical trial. Benef Microbes, 2018. **9**(4): p. 593-602.
[63]. Zhu, C., et al., The Predictive Potentiality of Salivary Microbiome for the Recurrence of Early Childhood Caries. Front Cell Infect Microbiol, 2018. **8**: p. 423.
[64]. Zhang, L., et al., Quantitative Analysis of Salivary Oral Bacteria Associated with Severe Early Childhood Caries and Construction of Caries Assessment Model. Sci Rep, 2020. **10**(1): p. 6365.
[65]. Arino, M., et al., Multicenter study on caries risk assessment in Japanese adult patients. J Dent, 2015. **43**(10): p. 1223-8.
[66]. Baker, J.L., et al., Klebsiella and Providencia emerge as lone survivors following long-term starvation of oral microbiota. Proc Natl Acad Sci U S A, 2019. **116**(17): p. 8499-8504.
[67]. Lima, A.B., et al., Pseudomonas spp. ISOLATED FROM THE ORAL CAVITY OF HEALTHCARE WORKERS FROM AN ONCOLOGY HOSPITAL IN MIDWESTERN BRAZIL. Rev Inst Med Trop Sao Paulo, 2015. **57**(6): p. 513-4.
[68]. Zdziarski, P., et al., Elizabethkingia miricola as an opportunistic oral pathogen associated with superinfectious complications in humoral immunodeficiency: a case report. BMC Infect Dis, 2017. **17**(1): p. 763.
[69]. Adachi, K., et al., Influence of Helicobacter pylori infection on periodontitis. J Gastroenterol Hepatol, 2019. **34**(1): p. 120-123.
[70]. Acharya, A., et al., Salivary IL-1β and red complex bacteria as predictors of the inflammatory status in sub-peri-implant niches of subjects with peri-implant mucositis. Clin Oral Implants Res, 2016. **27**(6): p. 662-7.
[71]. Ahmad, Z., et al., Role of Streptococcus pneumoniae OM001 operon in capsular polysaccharide production, virulence and survival in human saliva. PLoS One, 2018. **13**(1): p. e0190402.
[72]. Perry, S.E., et al., The association between oral bacteria, the cough reflex and pneumonia in patients with acute stroke and suspected dysphagia. J Oral Rehabil, 2020. **47**(3): p. 386-394.
[73]. Derafshi, R., et al., Isolation and Identification of Nonoral Pathogenic Bacteria in the Oral Cavity of Patients with Removable Dentures. J Int Soc Prev Community Dent, 2017. **7**(4): p. 197-201.
[74]. Azzi, L., et al., Helicobacter pylori in periodontal pockets and saliva: a possible role in gastric infection relapses. J Biol Regul Homeost Agents, 2017. **31**(1): p. 257-262.
[75]. Eventov-Friedman, S., et al., Saliva Real-Time Polymerase Chain Reaction for Targeted Screening of Congenital Cytomegalovirus Infection. J Infect Dis, 2019. **220**(11): p. 1790-1796.

[76]. Dworzański, J., et al., Prevalence of Epstein-Barr virus, human papillomavirus, cytomegalovirus and herpes simplex virus type 1 in patients with diabetes mellitus type 2 in south-eastern Poland. PLoS One, 2019. **14**(9): p. e0222607.
[77]. Derafshi, R., et al., PCR Detection of HHV8 DNA in the Saliva of Removable Denture Wearers Compared to Dentate Cases in Shiraz, South of Iran. Biomed Res Int, 2020. **2020**: p. 9358947.
[78]. Aoki, R., et al., Human herpesvirus 6 and 7 are biomarkers for fatigue, which distinguish between physiological fatigue and pathological fatigue. Biochem Biophys Res Commun, 2016. **478**(1): p. 424-430.
[79]. Auguste, A., et al., Prevalence of oral HPV infection among healthy individuals and head and neck cancer cases in the French West Indies. Cancer Causes Control, 2017. **28**(11): p. 1333-1340.
[80]. Devaraja, K., et al., Clinico-pathological peculiarities of human papilloma virus driven head and neck squamous cell carcinoma: A comprehensive update. Life Sci, 2020. **245**: p. 117383.
[81]. Albert, E., et al., Kinetics of torque teno virus DNA load in saliva and plasma following allogeneic hematopoietic stem cell transplantation. J Med Virol, 2018. **90**(9): p. 1438-1443.
[82]. Ayers, V.B., et al., infection and transmission of Cache Valley virus by Aedes albopictus and Aedes aegypti mosquitoes. Parasit Vectors, 2019. **12**(1): p. 384.
[83]. Dong, S., et al., Infection pattern and transmission potential of chikungunya virus in two New World laboratory-adapted Aedes aegypti strains. Sci Rep, 2016. **6**: p. 24729.
[84]. Balachandar, V., et al., COVID-19: emerging protective measures. Eur Rev Med Pharmacol Sci, 2020. **24**(6): p. 3422-3425.
[85]. Andersson, N., et al., Camino Verde (The Green Way): evidence-based community mobilisation for dengue control in Nicaragua and Mexico: feasibility study and study protocol for a randomised controlled trial. BMC Public Health, 2017. **17**(Suppl 1): p. 407.
[86]. Andries, A.C., et al., Value of Routine Dengue Diagnostic Tests in Urine and Saliva Specimens. PLoS Negl Trop Dis, 2015. **9**(9): p. e0004100.
[87]. Amado Leon, L.A., et al., Longitudinal Study of Hepatitis A Infection by Saliva Sampling: The Kinetics of HAV Markers in Saliva Revealed the Application of Saliva Tests for Hepatitis A Study. PLoS One, 2015. **10**(12): p. e0145454.
[88]. Ahmadi-Motamayel, F., et al., Evaluation of Salivary Melatonin Levels in HIV-positive Patients: A Historical Cohort Study. Rev Recent Clin Trials, 2017. **12**(3): p. 168-173.
[89]. Ayouni, S., et al., Relationship between GII.3 norovirus infections and blood group antigens in young children in Tunisia. Clin Microbiol Infect, 2015. **21**(9): p. 874.e1-8.
[90]. Costantini, V.P., et al., Epidemiologic, Virologic, and Host Genetic Factors of Norovirus Outbreaks in Long-term Care Facilities. Clin Infect Dis, 2016. **62**(1): p. 1-10.
[91]. Bockelman, C., et al., Mumps: An Emergency Medicine-Focused Update. J Emerg Med, 2018. **54**(2): p. 207-214.
[92]. Dhayhi, N.S., et al., First confirmed case of local human rabies in Saudi Arabia. Int J Infect Dis, 2019. **87**: p. 117-118.
[93]. Ayouni, S., et al., Rotavirus P[8] Infections in Persons with Secretor and Nonsecretor Phenotypes, Tunisia. Emerg Infect Dis, 2015. **21**(11): p. 2055-8.
[94]. Amraoui, F., M. Vazeille, and A.B. Failloux, French Aedes albopictus are able to transmit yellow fever virus. Euro Surveill, 2016. **21**(39).
[95]. Alejo-Cancho, I., et al., Twenty-four cases of imported zika virus infections diagnosed by molecular methods. Diagn Microbiol Infect Dis, 2016. **86**(2): p. 160-2.
[96]. Dirlikov, E., et al., Clinical Features of Guillain-Barré Syndrome With vs Without Zika Virus Infection, Puerto Rico, 2016. JAMA Neurol, 2018. **75**(9): p. 1089-1097.

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Table 1. List of human saliva microbiome related to Oral diseases as analysed by a conventional method

Commensal	Dental Caries	Periodontal Infection	Peri-implant Infection
	Candida albicans [10] C. dubliniensis [9]		Candida albicans[59, 60]
	Gram-positive bacteria		
	Actinomyces [16] [60]	Actinomycetes A. dentalis, A. naeslundii [12] [17]	Actinomyces naeslundii [59, 60]
		Aggregatibacter actinomycetemcomitans [12, 61]	
		Bacillus subtilis [13]	Bacillus subtilis [25]
	Bifidobacterium lactis [62]		
		Bacteroides [15] [16]	
	Capnocytophaga sp. C. leadbetteri [63]	Capnocytophaga sp C. leadbetteri [14] [15]	Dolosigranulum species [25]
	Staphylococcus aureus S. epidermidis [13]	S. aureus S. epidermidis [12]	S. aureus [23]
		Corynebacterium argentoratense [12] C. matruchotii [14]	
	Lactobacillus spp. L. fermentum L. rhamnosus [64] [62] [11]		
	Lautropia species[63]	Lautropia species[14]	Lautropia species[25]
		Enterococcus faecalis [26]	
Streptococcus [4]	Streptococcus anginosus S. intermedius S. mitis S. mutans [9] [26, 65]	Streptococcus anginosus S. intermedius S. mitis S. mutans [14, 15, 17]	
	Gram-negative bacteria		
			Enterobacter sp. [23]
			Escherichia coli[23]
			Klebsiella oxytoca K. pneumonia [23] [66]
		Pseudomonas aeruginosa P. fluorescens P. stutzeri [12, 67] [12, 15]	Pseudomonas aeruginosa P. fluorescens P. stutzeri [23]
	Leptotrichia L. buccalis L. hofstadii [63]	Leptotrichia L.buccalis L. hofstadii [14]	
		Dialister pneumosintes [15]	
Prevotella [4]	Prevotella P. denticola P. pallens [64] [63]	Prevotella [14]	
		Elizabethkingia miricola [68]	
Fusobacterium [4]	Fusobacterium [63]	Fusobacterium [63] [17] [14]	
		Haemophilus [17]	
		Helicobacter pylori [69]	
Neisseria [4]		Neisseria N. elongate[17] [15] [15]	
		Pigmentiphaga[17]	
		Porphyromonas gingivalis [61]	Porphyromonas

			gingivalis[70]
		Tannerella forsythensis [12]	Tannerella forsythia[70]
		Treponema parvum [15] Treponema sp. oral taxon [14]	Treponema denticola[70]
Veillonella [4]		Veillonella [17]	

Table 2. Association between opportunist salivary microbiome with specific systemic disease

Disease	**group**	**species**
Diabetes	yeast	Candida albicans [20] C.glabrata [20]
	Gram +	Staphylococcus, Streptococcus*, S. mitis, Clostridia sp [17]
	Gram -	Escherichia,Fusobacterium , Haemophilus, Pigmentiphaga, Veillonella* [17]
Respiratory Infection Cystic fibrosis	Yeast	Candida albicans, C. tropicalis [18]
	Gram +	Actinomycetes, Streptococcus pneumonia [71]
	Gram -	Escherichia coli, Klebsiella pneumonia [72] [27]
Skin infection	Yeast	nd
	Gram +	Staphylococcus epidermidis [27]
	Gram -	Pseudomonas stutzeri [67]
AIDS	Yeast	nd
	Gram +	Streptococcus mitis [15]
	Gram -	Capnocytophaga sp, Dialister pneumosintes, Proteobacteria [15]
Local & systemic infection	Yeast	nd
	Gram +	Enterococcus faecalis, Staphylococcus hominis [27]
	Gram -	Proteobacteria [16]
Cystic fibrosis	Yeast	nd
	Gram +	Mycobacterium abscessus [28]
	Gram -	Pseudomonas aeruginosa [28]
Liver abscesses	Yeast	nd
	Gram +	Streptococcus anginosus [27]
	Gram -	Klebsiella pneumoniae [27]
Non-oral pathogen bacteria	Yeast	nd
	Gram +	nd
	Gram -	Pseudomonas aeroginosa, Kluyvera spp. E. coli, Enterobacter aerogenes, E. cloacae, E. kobei [73]
Nosocomial pathogen	Yeast	nd
	Gram +	nd
	Gram -	Pseudomonas aeruginosa [29], Klebsiella oxytoca [66]
Gastric Infection	Yeast	nd
	Gram +	nd
	Gram -	Helicobacter pylori [74]

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Table 3. List of salivary virus

Virus	Sites	Ref.
DNA Virus		
Congenital cytomegalovirus (CMV)	Newborns	[75]
Epstein-Barr virus (EBV)	Stomach, intestine	[76]
Human herpesvirus	Skin	[77] [78]
Human papillomavirus (HPV)	Skin	[79] [80]
Torque Teno virus (TTV) DNA	Plasma	[81]
RNA Virus		
Cache Valley virus (CVV)	Human brain	[82]
Chikungunya virus (CHIKV)	Brain, liver, joint, bone	[83]
COVID-19	Respiratory tract	[84]
Dengue virus	Red blood cells	[85] [86]
Hepatitis A virus (HAV)	liver	[87]
Human immunodeficiency virus (HIV)	Blood, CNS	[88]
Noroviruses (NoVs)	Gastric	[89] [90]
Paramyxoviridae virus	Mumps, salivary glands	[91]
Rabies	zoonotic viral infection	[92]
Rotavirus	Gastric	[93]
yellow fever virus (YFV)	Gastric, intestine	[94]
Zika virus (ZIKV)	Nerve cells	[95] [96]

MICROBIOME DIVERSITY IN THE SALIVA RELATED ORAL AND SYSTEMIC DISEASES

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