Chapter 11
Salivary Diagnosis of Infectious Diseases

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11.1 Introduction

Systemic infectious diseases can be associated in some cases with high mortality rates. Thus, there is a need for early detection and diagnosis in order to initiate an appropriate treatment regime as soon as possible (Farnaud et al. 2010). Nowadays, the diagnosis of infectious diseases is still dependent on the evaluation of blood and/or tissue samples. Although they are effective, these procedures are invasive and expensive, moreover, depending on different clinical conditions, these types of tests may not be accessible for many patients and health care providers (Yoshizawa et al. 2013). For all these reasons saliva-based diagnostics have been the primary focus of investigation for a variety of infectious pathogens for several years (Farnaud et al. 2010).

The method of detection of an infection could be either direct – detection of the pathogen or its nucleic acids (DNA or RNA), or indirect – detection of host salivary antibodies IgA, IgM or IgG against the pathogen. The use of one or other type of methodology would vary depending on the specific pathogen; for example, direct detection of Mycobacterium tuberculosis in saliva by culture was less effective than the detection of bacterial DNA by PCR (17% vs. 98%) (Farnaud et al. 2010).

The aim of this chapter is to review the main methods that have been developed and evaluated in saliva for the diagnostic and monitoring of systemic infectious diseases of humans and domestic animals.

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11.2 Salivary Diagnostics of Human Infectious Diseases

A brief summary of saliva-based methods developed for the detection of selected infectious pathogens affecting humans is presented in Table 11.1.

Table 11.1 Overview of selected publications describing methods for the diagnosis of infectious diseases using saliva as a sample

Pathogen	Biomarker	References
HIV	IgG	Scully and Samaranayake (1992), Cordeiro et al. (1993), Scully (1997) and Martínez et al. (1999)
	IgA	Matsuda et al. (1993)
Hepatitis A virus	Total and IgM	Thieme et al. (1992)
	IgG	Ahmed et al. (2011)
	RNA	Mackiewicz et al. (2004)
Hepatitis B virus	Total and Ig M	Scully and Samaranayake (1992) and Thieme et al. (1992)
Hepatitis C virus	Total and Ig M	Scully and Samaranayake (1992) and Thieme et al. (1992)
	Total	Cha et al. (2013)
Dengue virus	IgG	Cuzzubbo et al. (1998), Balmaseda et al. (2003, 2008) and Vázquez et al. (2007)
	IgM	Cuzzubbo et al. (1998), Balmaseda et al. (2003, 2008), Vázquez et al. (2007) and Chakravarti et al. (2007)
	IgA	Balmaseda et al. (2003, 2008), Vázquez et al. (2007) and Yap et al. (2011)
	RNA	Torres et al. (2000), Balmaseda et al. (2008) and Poloni et al. (2010)
Ebola viruses	RNA	Formenty et al. (2006) and Bausch et al. (2007)
Zika virus	RNA	Musso et al. (2015)
Measles virus	IgG	Perry et al. (1993), Garrido Redondo et al. (1997), Gill et al. (2002), Kremer and Muller (2005) and Vainio et al. (2008)
	IgM	Perry et al. (1993), Brown et al. (1994) and Hutse et al. (2010)
	IgA	Garrido Redondo et al. (1997)
	RNA	Jin et al. (2002) and Hutse et al. (2010)
Mumps virus	IgG	Perry et al. (1993) and Vainio et al. (2008)
	IgM	Perry et al. (1993) and Warrener and Samuel (2006)
	RNA	Jin et al. (2002)
Rubella virus	IgG	Parry et al. (1987), Perry et al. (1993), Nokes et al. (1998), Ramsay et al. (1998), Vyse et al. (1999), Christopher Maple and Jones (2002) and Ben Salah et al. (2003)
	IgM	Centers for Disease Control and Prevention (CDC) (2008) and Lambert et al. (2015)
	RNA	Vyse et al. (1999), Jin et al. (2002), Abernathy et al. (2009) and Vauloup-Fellous et al. (2010)
Helicobacter pylori	IgG	Loeb et al. (1997) and Luzza and Pallone (1997)
	DNA	Jiang et al. (1998) and Anand et al. (2014)

11.2.1 Viral Diseases

11.2.1.1 Human Immunodeficiency Virus (HIV)

Two types of human Immunodeficiency Viruses are described, HIV-type 1 (HIV-1) and HIV-type 2 (HIV-2). The main agent of acquired immune deficiency syndrome is HIV-1 and is a related member of the Lentivirus genus of the *Retroviridae* family (Fanales-Belasio et al. 2010). Traditionally, HIV infection have been performed through antibody detection in serum or plasma and thus, require trained personnel for collection and involves a high risk of transmission (Martínez et al. 1999). Saliva tests for HIV detection have been reported to be a noninvasive alternative to the quantification of antibodies in blood (Lawrence 2002). Different assay formats have been developed in which whole saliva was used for detecting antibodies directed against specific HIV viral protein epitopes with high sensitivity (98–100%) and specificity (97–100%) (Scully and Samaranayake 1992; Scully 1997). Furthermore, in one study that uses an enzyme-linked fluorescence technique combined with Western blot, saliva showed better sensitivity and specificity than serum (Martínez et al. 1999). In addition, it has been suggested that salivary detection of IgA may be useful with prognostic purposes, since salivary IgA levels to HIV decrease when infected patients show symptoms, thus indicating the evolution of the infection (Matsuda et al. 1993).

Although different tests have been developed in saliva and oral fluid, there is only one FDA- approved, commercially available testing system, for public use (OraSure®). It detects antibodies against the p24 antigen of HIV and consists of a cotton pad connected to a nylon stick and a vial that contains a preservative solution (Malamud 1997). The samples collected with OraSure® device could have IgG concentrations three to fourfold higher than those usually found in whole saliva (Cordeiro et al. 1993) and the storage solution maintain sample stability overtime at similar levels than initial concentrations (Malamud 1997). Additionally, the storage solution has been reported that inhibits different strains of HIV (Bestwick and Fitchen 1997) further increasing the safety of this method.

11.2.1.2 Hepatitis

Viral hepatitis constitutes an important public health problem all over the world. Hepatitis A (HAV), is caused by a virus of the *Picornaviridae* family and contamination of water supply and food is considered as the main sources of transmission (Oba et al. 2000). This type of hepatitis is one of the most frecuent causes of infectious hepatitis in the world. In contrast, Hepatitis B virus (HBV) and hepatitis C virus (HCV) are frequently related with chronic disease and can ultimately cause severe liver-related complications such as cirrhosis and hepatocellular carcinoma. Although infection is quite common, most patients do not show symptoms which implies a high potential risk of progression and transmission of the disease (Yoshizawa et al. 2013).

Traditional diagnosis and monitoring of viral hepatitis consist mainly on blood-based serological tests determining viral load as well as viral antibodies and antigens; however it has been described that antigens and/or antibodies for hepatitis A, B, and C viruses can be detected in the salivary samples of infected individuals (Amado et al. 2006) and, thus, saliva has been suggested as a useful alternative to serum for the diagnosis of variants of viral hepatitis. HAV can be diagnosed with 100% sensitivity and 98% specificity based on the presence of IgM antibodies in saliva (Thieme et al. 1992). Comparison of serum and saliva levels of antibody to HAV revealed excellent agreement (Thieme et al. 1992). Furthermore, it has been demonstrated that the determination of salivary IgG concentrations is useful to evaluate the efficacy of HAV immunizations (Ahmed et al. 2011). Not only antibody detection but also RNA detection in saliva has been suggested as a useful marker for tracing and monitoring HAV infection in community settings (Mackiewicz et al. 2004).

Similarly to HAV, analysis of saliva is highly sensitive and specific for the diagnosis of viral hepatitis B as well as hepatitis C with a sensitivity and specificity approaching 100% (Scully and Samaranayake 1992; Thieme et al. 1992). These findings suggest a potential role for saliva as a noninvasive mode of HBV and HCV diagnosis and disease state monitoring (Yoshizawa et al. 2013). Even, a commercially available rapid test (OraQuick® HCV test) has been developed and evaluated with saliva showing a sensitivity and specificity of 97.8% and 100%, respectively, by this supporting the utility of rapid testing using oral fluid in various medical and non-medical settings (Cha et al. 2013).

11.2.1.3 Dengue

Dengue virus (DENV) is an arthropod-borne flavivirus mainly transmitted by mosquito vectors (Guzman and Harris 2015). It has been described five antigenically distinct dengue viruses, DENV1-DENV5, that can cause dengue fever and severe dengue (Mustafa et al. 2015). Different tests have been developed for the clinical diagnosis of the disease that detect the virions, nucleic acids, antibodies, or antigenic components of a DENV infection (Wasik et al. 2018).

Literature shows that various antibodies such as IgA, IgM, IgE are detectable in the diagnosis of Dengue on using saliva with variable sensitivities and specificities (from 39% to 100%) (Cuzzubbo et al. 1998; Balmaseda et al. 2003, 2008; Vázquez et al. 2007). It has been described that salivary IgG levels could be used to distinguish between primary and secondary dengue virus infections (Cuzzubbo et al. 1998) and, although detection of IgG in saliva was less sensitive than in serum or filter-paper blood spots, it is considered an acceptable and useful marker for community-based studies, because of its non-invasive nature (Ravi Banavar and Vidya 2014). Therefore, saliva was considered a promising sample for dengue diagnostics (Chakravarti et al. 2007). In addition, the utility of saliva in an assay that detects DENV-specific IgA in the early phase of a 2nd dengue infection shows 100% sensitivity and 97% specificity from the day-one after fever onset with a good correlation to IgA levels in serum (Yap et al. 2011). Besides the specific antibodies, DENV RNA has also been found in saliva by RT-PCR (Torres et al. 2000). Furthermore, in

case reports analyzing acute infections, the detection of DENV in saliva by RT-PCR as well as the application of filter-paper for saliva sampling, prove the usefulness of these non-invasive samples (Balmaseda et al. 2008; Poloni et al. 2010).

11.2.1.4 Ebola

Ebola viruses contain a single-stranded RNA genome that encodes seven viral proteins. Different methods for detecting Ebola infection and/or disease have been developed for use in clinical laboratory settings that can be grouped into three categories: serologic tests, antigen tests that detect viral proteins, and molecular tests that detect viral RNA (Strong et al. 2006; Broadhurst et al. 2016). Antigen detection and molecular tests have demonstrated to be very effective for acute diagnosis, however, serology is minimally useful as a diagnostic tool in the acute setting (Broadhurst et al. 2016).

Ebola virus, as well as other viral hemorrhagic fevers, are mostly detected in blood derived samples such as whole blood, plasma or serum although different studies reported Ebola detection also in body fluids including saliva (Niedrig et al. 2018).

There are only one reported study in which antibodies against Ebola has been investigated in saliva but it failed to detect antibodies in the oral fluid specimens obtained from seropositive patients as based on serum analyses (Formenty et al. 2006). In contrast, RT-PCR was effective to detect RNA of the virus in saliva (Formenty et al. 2006; Bausch et al. 2007). Furthermore, higher mortality was reported among patients with RT-PCR-positive saliva, suggesting that it can be an indicator of a poor prognosis (Bausch et al. 2007). Although detection of Ebola virus by RT-PCR in oral fluid specimens is sufficiently reliable as a diagnostic tool, especially in the investigation of the outbreak of Ebola, blood samples are still necessary to analyse the biological status and immune response of the patient and to optimize treatment plan (Shanbhag 2015).

Further studies are necessary to improve laboratory methods to detect suspected cases early and to design more-sensitive screening of the disease. However, it has been suggested that the use of oral fluid samples could make earlier detection of outbreaks much easier (Shanbhag 2015; Niedrig et al. 2018).

11.2.1.5 Zika

Zika virus (ZIKV) is an arthropod-borne virus (arbovirus) of the family *Flaviviridae* and genus *Flavivirus* (Musso and Gubler 2016). Laboratory Zika fever diagnosis is challenging because there is no "gold standard" diagnosis tool. The cross reactivity of antibodies between Flaviviruses, limits the use of serology, viral culture is not routinely performed and there is no antigenic detection test available (Musso et al. 2015).

ZIKV RNA has been identified in saliva samples increasing the molecular detection rate of ZIKV in acute cases, but ZIKV did not persist for a longer time frame in saliva as in urine or semen (Musso et al. 2015). The inconsistency of saliva makes

urine the most reliable and utilized secondary sample type ('WHO | Laboratory testing for Zika virus infection' 2016; Bingham et al. 2016) and a combination of samples (blood/urine and saliva) has been recommended to increase the sensitivity of the virus detection (Musso et al. 2015; Zhang et al. 2016).

11.2.1.6 Measles, Mumps and Rubella

The detection of measles, mumps and rubella (MMR) antibodies in saliva represent the most advanced application to the diagnostic utility of saliva in case of infectious diseases since a MMR salivary surveillance program has already been successfully running in the United Kingdom from 1994 (Madar et al. 2002).

Measles virus (MV) is a negative single-stranded RNA virus, belonging to the genus *Morbillivirus*, of the family *Paramyxoviridae* (Bellini et al. 1994). Laboratory confirmation of measles cases is an essential aspect of surveillance at all stages of control programs because clinical diagnosis is unreliable (Featherstone et al. 2003). The mainstay of laboratory confirmation is the detection of measles-specific IgM antibodies in serum samples (Centers for Disease Control and Prevention (CDC) 2008). Several studies have shown that saliva samples may be adequate substitutes to serum for the detection of measles specific IgG and IgM antibodies (Perry et al. 1993; Brown et al. 1994; Garrido Redondo et al. 1997; Gill et al. 2002; Kremer and Muller 2005; Vainio et al. 2008; Hutse et al. 2010) and viral RNA (Jin et al. 2002; Hutse et al. 2010). Saliva based assays for measles elimination program in Europe have been increasingly introduced as a good alternative to blood being recommended by WHO (Ramsay et al. 1997; Centers for Disease Control and Prevention (CDC) 2008).

The causative agent of mumps, the mumps virus, belongs to the family *Paramyxoviridae*, subfamily *Paramyxovirinae*, genus *Rubulavirus* (Maple 2015). Different radioimmunoassays and enzyme immunoassays have been developed to detect specific IgG or IgM (Perry et al. 1993; Warrener and Samuel 2006; Vainio et al. 2008) in saliva and detection of mumps RNA in oral fluid samples collected during the first 14 days after onset of symptoms is also possible (Jin et al. 2002). In comparison with blood based detection methodologies, most of the mumps oral fluid assays reported had acceptable sensitivity (79–94%) and specificity (94–100%) (Maple 2015).

The rubella virus is a positive-sense, single-stranded RNA virus that belongs to the family *Togaviridae* and is the only member of the genus *Rubivirus* (Maple 2015). Different radioimmunoassays and enzyme immunoassays (GACRIA, GACELISA, EIA) have been developed to detect IgG in saliva with variable reported sensitivity and specificity (Parry et al. 1987; Perry et al. 1993; Nokes et al. 1998; Ramsay et al. 1998; Vyse et al. 1999; Ben Salah et al. 2003) but a reduced assay sensitivity with age was reported for IgG in some cases (Nokes et al. 1998; Ramsay et al. 1998). In addition, a rubella IgG time-resolved fluorescence immunoassay was described with promising results in saliva (Christopher Maple and Jones 2002). Saliva-based assays for rubella IgM detection were more established (Centers for Disease Control and Prevention (CDC) 2008; Lambert et al. 2015) and used in rubella surveillance and control (Maple 2015). In addition to antibody testing, oral

fluids, if properly collected and stored can be useful to detect rubella virus genome by RT-PCR and to complement the results of antibody testing (Vyse et al. 1999; Jin et al. 2002; Vauloup-Fellous et al. 2010). Furthermore, one study (Abernathy et al. 2009), showed that rubella RT-PCR performed in saliva can detect more cases than IgM analysis of oral fluid samples or even serum collected in the initial 2 days after the outbreak. However, the combination of rubella RT-PCR and serology allow the confirmation of the highest number of rubella cases.

11.2.1.7 Other Viral Diseases

An antibody capture radioimmunoassay (GACRIA) to detect IgG to Epstein-Barr virus (EBV) viral capsid antigen (VCA) in saliva has been developed and has sufficient sensitivity to be used for epidemiological screening and enable testing for anti-EBV VCA on a wide scale (Vyse et al. 1997). The salivary IgA response against Rotavirus in newborn infants was found to be a better marker of rotavirus infection than the serum antibody response (Aiyar et al. 1990). PCR based identification of Herpes simplex virus type-1 (HSV-1) DNA in saliva is a useful method for the early detection of its reactivation that is involved in the pathogenesis of Bell's palsy (Lazarini et al. 2006).

11.2.2 Bacterial Diseases

Helicobacter pylori (*H. pylori*) is a Gram-negative, microaerophilic bacterial pathogen that usually grows in the stomach mucus. *H. pylori* infection is the strongest risk factor for developing gastric and duodenal ulcers (peptic ulcer disease) in humans and, it may also play a role in gastric cancer (Kountouras and Walt 1998; Gisbert 2015). Attempts have been made to use saliva as a diagnostic aid for peptic ulcer disease. ELISA assays for detection of salivary IgG antibodies against *H. pylori* have been developed (Loeb et al. 1997; Luzza and Pallone 1997). However, despite some interesting results the assays used had limited diagnostic value and should be improved. The use of PCR is more effective for the detection of *H. pylori* in the saliva (Jiang et al. 1998; Anand et al. 2014).

Saliva from patients with a variety of other disorders including Pneumococcal pneumonia, shigellosis, pigeon breeders disease, neurocysticercosis and Lyme disease have been evaluated for the presence of specific antibodies, with variable results (Kaufman and Lamster 2002; Kumar Nagarajappa and Bhasin 2015).

11.3 Salivary Diagnostics of Animal Infectious Diseases

A brief summary of saliva-based methods developed for the detection of selected infectious pathogens affecting domestic species is presented in Table 11.2.

Table 11.2 Saliva-based biomarkers investigated for selected pathogens affecting domestic species

Species	Pathogen	Sample	Biomarker	References
Dog	*Helicobacter* spp.	Saliva	DNA	Ekman et al. (2013)
		Oral swab		Recordati et al. (2007), Chung et al. (2014) and Jankowski et al. (2016, 2017)
	Leishmania infantum	Saliva	IgG2, IgA	Cantos-Barreda et al. (2017)
		Oral swab	DNA	Lombardo et al. (2012), de Almeida Ferreira et al. (2013) and Aschar et al. (2016)
	Rabies virus	Oral swab	RNA	Wacharapluesadee et al. (2012)
		Saliva	Rabies virus antigen RNA	Kasempimolporn et al. (2011) and Zhang et al. (2017)Saengseesom et al. (2007) and Kasempimolporn et al. (2011)
Cat	Feline calicivirus (FCV)	Oropharingeal swab	RNA	Helps et al. (2002), Abd-Eldaim et al. (2009) and Druet and Hennet (2017)
	Feline immunodeficiency virus (FIV)	Oral swab	Salivary antibodies against FIV, RNA, proviral DNA	Chang-Fung-Martel et al. (2013), Westman et al. (2016) and Miller et al. (2017)
		Saliva	RNA Proviral DNA	Matteucci et al. (1993)
	Feline leukemia virus (FeLV)	Oral swab	FeLV p27 antigen	Westman et al. (2017)
			Proviral DNA	Cavalcante et al. (2018)
Cattle	Foot-and-mouth-disease (FMD) virus	Saliva	IgA	Archetti et al. (1995)
	Schmallenberg virus	Saliva	IgG, IgA	Lazutka et al. (2015)
Pig	African swine fever virus (ASFV)	Saliva	Specific antibodies	Mur et al. (2013)
			RNA	Lung et al. (2018)
	Actinobacillus pleuropneumoniae	Saliva	IgM, IgG, IgA	González et al. (2017)
			DNA	Cheong et al. (2017)
	Classical swine fever virus (CSFV)	Saliva	IgG and IgA	Panyasing et al. (2018)
			RNA	Dietze et al. (2017), Huang et al. (2017), Petrini et al. (2017) and Lung et al. (2018)

(continued)

Table 11.2 (continued)

Species	Pathogen	Sample	Biomarker	References
	Erysipelothrix rhusiopathiae	Saliva	IgM, IgG, DNA	Giménez-Lirola et al. (2013)
	FMD virus	Saliva	RNA	Lung et al. (2018)
	Haemophilus parasuis	Saliva	DNA	Cheong et al. (2017)
	Influenza A virus (IAV)	Saliva	IAV nucleoprotein antibodies; RNA DNA/RNA	Gerber et al. (2017)
			RNA	Ramírez et al. (2012), Decorte et al. (2015), Biernacka et al. (2016) and Hernández-García et al. (2017)
	Mycoplasma hyopneumoniae	Saliva	DNA	Cheong et al. (2017), Hernández-García et al. (2017) and Pieters et al. (2017)
	Mycoplasma hyorhinis	Saliva	DNA	Cheong et al. (2017)
	Pasteurella multocida	Saliva	DNA	Cheong et al. (2017)
	Porcine circovirus type 2 (PCV2)	Saliva	RNA	Ramírez et al. (2012)
			DNA	Cheong et al. (2017) and Hernández-García et al. (2017)
	Porcine reproductive and respiratory syndrome (PRRS) virus	Saliva	PRRSV-antibodies	Langenhorst et al. (2012), Olsen et al. (2013), Kuiek et al. (2015) and Biernacka et al. (2016)
			IgG and IgA	Decorte et al. (2014) and Gerber et al. (2014)
			IgG	Kittawornrat et al. (2013) and Ouyang et al. (2013)
			IgG, IgA and IgM	Olsen et al. (2013)
			RNA PRRSV-specific neutralizing antibodies	Ramírez et al. (2012), Biernacka et al. (2016), Cheong et al. (2017) and Hernández-García et al. (2017)
		Oral swab and saliva	PRRSV-specific antibodies	Sattler et al. (2015)
	Streptococcus suis	Saliva	DNA	Cheong et al. (2017)
	Swine vesicular disease virus (SVDV)	Oral fluid	RNA	Lung et al. (2018)

11.3.1 Dogs

11.3.1.1 *Helicobacter* spp. Infection

The presence of gastric *Helicobacter* spp. is relatively frequent in dogs with gastritis and chronic vomiting (61–100%), and also in clinically healthy dogs (67–86%). *H. heilmannii* is the most prevalent species of gastric *Helicobacter* spp. in the saliva of dogs (73.3%) (Jankowski et al. 2016). This domestic animal constitutes a reservoir of *Helicobacter* spp. and a risk factor for human non-*pylori Helicobacter* spp. infection (Meining et al. 1998).

Diagnostic methods for *Helicobacter* spp. infection have been traditionally divided into invasive and non-invasive methods. Regarding invasive methods, *Helicobacter* spp. organisms from biopsied samples are usually visualized in stains, and the culture of the biopsied sample is considered the "gold standard" (Fox et al. 1995). About the non-invasive methods, saliva samples and oral swabs have been used as specimens for detection of *Helicobacter* spp. infection in dogs by PCR (Recordati et al. 2007; Ekman et al. 2013; Chung et al. 2014; Jankowski et al. 2016, 2017). Although *Helicobacter* spp. was found in the saliva of a high percentage of dogs with gastritis (76.6%), this percentage was still lower than that obtained on gastric biopsies (100%) (Jankowski et al. 2017).

11.3.1.2 Leishmaniosis

Canine leishmaniosis (CanL) is a zoonotic disease caused by the protozoan parasite *Leishmania infantum* (syn. *L. chagasi* in the New World) in the Mediterranean basin, China, and Central and South America. Domestic dogs constitute the main reservoir of infection for humans, which can develop visceral leishmaniosis (VL) (Moreno and Alvar 2002; Gramiccia and Gradoni 2005). *Leishmania*-infected dogs can remain asymptomatic or develop visceral disease due to immune-complexes deposition. Skin lesions are the most frequent clinical sign found on a physical examination (Baneth and Aroch 2008; Solano-Gallego et al. 2009).

Diagnosis of CanL had been traditionally performed by detection of specific serum antibodies against *Leishmania* spp. or detection of *Leishmania* spp. DNA in different tissues. The most frequently used quantitative serological techniques for the detection of anti-*Leishmania* antibodies are based on the enzyme-linked immunosorbent assay (ELISA) and the immunofluorescence antibody test (IFAT). Immunochromatographic tests provide rapid qualitative results but show a lack of sensitivity (Solano-Gallego et al. 2011). Detection of *Leishmania* spp. DNA by PCR allows high-sensitivity diagnosis (until 0.001 parasites per PCR reaction) (Francino et al. 2006). Lymph node, bone marrow, spleen and skin biopsies provide high-sensitivity results in detection of *Leishmania* spp. infection in both symptomatic or asymptomatic dogs (Maia and Campino 2008; Miró et al. 2008). However, these samples are obtained through invasive procedures that cause stressful situations for the animal and less acceptance by the owner.

Recently, a novel high-sensitive assay for the serological diagnosis of CanL based on the time-resolved immunofluorescence (TR-IFMA) have been developed and validated. This TR-IFMA quantifies the anti-*Leishmania* IgG2 and IgA antibody levels in saliva from dogs with CanL. This assay shows an adequate precision, analytical sensitivity, and accuracy; and greater differences between *Leishmania*-seropositive and *Leishmania*-seronegative dogs than a commercial ELISA in serum. Determination of anti-*Leishmania* IgA levels has less diagnostic value than IgG2. These findings highlight the potential of measuring anti-*Leishmania* IgG2 in canine saliva to diagnose CanL taking advantage of a high-sensitive method and a non-invasive specimen (Cantos-Barreda et al. 2017). Moreover, the potential use of measuring levels of anti-*Leishmania* IgG2 in saliva for treatment monitoring of CanL have been reported (Cantos-Barreda et al. 2018). In addition, alternatively to the use of invasive samples for detection of *Leishmania* spp. DNA by PCR, some authors have investigated the diagnostic utility of using oral swabs. However, the sensitivity of the qPCR in oral swabs is lower than in invasive samples such as bone marrow, lymph node or skin biopsies due to the low parasite burden in mucosae (de Almeida Ferreira et al. 2013; Lombardo et al. 2012; Aschar et al. 2016).

11.3.1.3 Rabies

Rabies is an infectious disease caused by a virus of the family *Rhabdoviridae* genus *Lyssavirus* mainly transmitted to humans by the bite of infected dogs in which this virus can cause fatal encephalitis (rabies) (Walker et al. 2019). Control through vaccination of dogs is effective in reducing the incidence of rabies (Rattanavipapong et al. 2019).

According to the World Health Organization (WHO 2005), the microscopic examination of the brain tissue stained using the direct fluorescent antibody (DFA) assay is the "gold standard" for post-mortem diagnosis of rabies. This technique involves open the skull of the dead animal to collect the brain. Furthermore, the fact that the brain tissue must be intact constitutes a limitation of the technique (Kamolvarin et al. 1993).

The presence of rabies virus in the saliva of infected dogs have been reported, even prior to the appearance of clinical signs (Vaughn et al. 1965). It has been shown that reverse transcriptase polymerase chain reaction (RT-PCR) from oral swabs or saliva exhibited high sensitivity (84.6–87%), but low than using brain tissue (100%) (Saengseesom et al. 2007; Wacharapluesadee et al. 2012). Detection of rabies virus antigen in the saliva has also been used for serological diagnosis of rabies. Zhang et al. (2017) developed an ELISA assay that detected positive rabies virus antigen in six of eight saliva samples from rabid dogs. In addition, Kasempimolporn et al. (2011) validated a rapid immunochromatographic assay for saliva samples with high sensitivity (93%) and specificity (94.4%) regarding the "gold standard" fluorescent antibody test (FAT) on brain smears. Moreover, this study also reported a nested polymerase chain reaction (nested-PCR) using saliva for the detection of rabies virus RNA with a sensitivity and specificity of 100% compared to the FAT results.

11.3.2 Cats

11.3.2.1 Feline Calicivirus Infection

Feline calicivirus (FCV) is a highly infectious pathogen of cats belonging to the family *Caliciviridae*. FCV mainly produce oral and upper respiratory tract disease, frequently occurring oral ulcerations and ocular and nasal discharges. However, vaccination against FCV has been reduced the incidence of disease (Radford et al. 2007).

Conjunctival and oropharyngeal swabs have been traditionally used to diagnose FCV through virus isolation. Application of RT-PCR for FCV RNA detection is reported to be as much sensitive as virus isolation (Helps et al. 2002) and has been extensively used to determine the FCV load in oropharyngeal swabs (Abd-Eldaim et al. 2009; Druet and Hennet 2017).

11.3.2.2 Feline Immunodeficiency

Feline immunodeficiency is an infectious disease affecting domestic cats all around the world caused by a lentivirus of the *Rhabdoviridae* family (Pedersen et al. 1989). Feline immunodeficiency virus (FIV) is primarily transmitted by biting and produces progressive immunosuppression as a consequence of affection of immune system cells. Consequently, cats become more prone to suffer opportunistic infections or cancer, and the outcome can be fatal (Yamamoto et al. 1988; Miller et al. 2017).

Detection of FIV antibodies using immunochromatographic tests is the most common diagnostic tool for FIV diagnosis in the veterinary clinic. However, these commercial snap tests are validated to be performed in serum, plasma or anticoagulated whole blood (Chang-Fung-Martel et al. 2013).

Saliva of FIV-infected cats contains infectious virus particles as well as salivary IgG antibodies that significantly increases over time (Miller et al. 2017), which could facilitate serological diagnosis using saliva samples. The ability of commercial immunochromatographic tests commercially validated in serum, plasma or whole blood specimens to diagnose FIV-infected cats via detection of salivary FIV antibodies has been evaluated. Despite the good specificity (98–100%), sensitivity is found to be lower in saliva samples (44–96%) than in the validated samples (Chang-Fung-Martel et al. 2013; Westman et al. 2016). Detection of FIV RNA in the saliva of cats by different types of PCR has also been reported (Matteucci et al. 1993; Westman et al. 2016; Miller et al. 2017).

11.3.2.3 Feline Leukemia

Feline leukemia virus (FeLV) belongs to the *Retroviridae* family and induces anemia and immunosuppression in infected cats (Cavalcante et al. 2018).

Antigen detection of the viral capsid protein (p27) has been traditionally used to detect cats with FeLV using serum, plasma or whole blood samples (Westman et al. 2017). Detection of this antigen has been usually performed using immunochromatographic tests (Hartmann et al. 2007; Sand et al. 2010).

Westman et al. (2016) evaluated the accuracy of three point-of-care FeLV p27 antigen tests commonly used for serological diagnosis of FeLV-infected cats. However, results derived from this study revealed that sensitivity for all the tests evaluated using saliva (54%) was lower than using whole blood (57–60%), suggesting that saliva is less suitable for p27 antigen detection in FeLV diagnosis. Proviral FeLV DNA was also detected by qPCR from oral swabs (Cavalcante et al. 2018).

11.3.3 Cattle

11.3.3.1 Foot-and-Mouth-Disease

Foot-and-mouth-disease (FMD) is a highly contagious disease caused by the FMD virus, an *Apthovirus* of the *Picornaviridae* family affecting all cloven-foot animals, including domestic ruminants and pig. Characteristic clinical signs are acute febrile reaction and the formation of vesicles in the mouth, tongue, hooves, and nipples (Alexandersen et al. 2003).

Archetti et al. (1995) reported a study in which oropharyngeal and saliva samples were tested by two types of ELISA tests in order to determine the best specimen and ELISA test for FMD-specific mucosal antibodies assessment. For diagnosis, the tissue of choice is epithelium or vesicular fluid. When epithelial tissue is not available, oesophageal-pharyngeal fluid samples can be collected for virus isolation (OIE 2004).

11.3.3.2 Schmallenberg Virus Infection

Schmallenberg virus (SBV) is a recently emerged orthobunyavirus that causes diarrhea, fever, malformations in offspring if fetal infection, and reduces milk yield in adult ruminants (Muskens et al. 2012; Conraths et al. 2013).

Detection of SBV-specific antibodies in tank milk samples using ELISA was widely used to determine the herd-levels exposure to SBV (Daly et al. 2015). However, testing milk samples not include males and young cattle in the analysis. In order to overcome this fact and taking advantage of saliva samples characteristics, Lazutka et al. (2015) developed an ELISA to detect IgG and IgA specific-SBV antibodies in saliva. Their IgG results from saliva showed close agreement with those obtained in serum and milk samples.

11.3.4 Pig

11.3.4.1 African Swine Fever

African swine fever (ASF) caused by a DNA virus member of the family *Asfarviridae*, the ASF virus (ASFV), is one of the most complex and lethal swine diseases and causes fever, abortus, erythema, pneumonia, pericarditis, or kidney hemorrhages, among other main lesions that can be observed in pigs with ASF (Sánchez-Vizcaíno et al. 2015).

Virological and serological detection is recommended to diagnose ASF. The most commonly used techniques for virological detection are virus isolation and haemadsorption (HAD) tests -which are considered the gold standard-, PCR, and direct immunofluorescence. The ELISA is the most commonly used serological test for ASF serological diagnosis. The samples of choose to diagnose ASF include serum, blood, spleen, lymph nodes, kidney, lung and bone marrow (Malmquist and Hay 1960; Sánchez-Vizcaíno et al. 2015).

ASFV-specific antibodies can also be detected in oral fluid samples of experimentally infected pigs with ASFV by ELISA and immunoperoxidase technique (IPT) (Mur et al. 2013). Results from that study lead to the conclusion that oral fluid samples could be a suitable alternative to blood as specimen to detect the presence of ASFV-specific antibodies.

11.3.4.2 Classical Swine Fever

Classical swine fever (CSF) is one of the most important diseases of swine and the causative agent is a virus (CSFV) from the family *Flaviviridae* genus *Pestivirus* (Blome et al. 2017; Petrini et al. 2017). This disease is characterized by unspecific clinical presentation like fever, anorexia, gastrointestinal symptoms, general weakness, and conjunctivitis (Petrov et al. 2014).

Detection of CSFV-specific antibodies is the best option for CSFV surveillance, however, the costs of collection blood samples are a limitation (Petrini et al. 2017). Alternatively, CSFV-specific IgG and IgA have been detected in oral fluid samples, reporting a cost-effective system for screening of populations for CSFV (Panyasing et al. 2018). Moreover, usage of oral fluid or oral swab samples for detection of CSFV RNA has been reported useful the diagnosis of this disease (Huang et al. 2017; Petrini et al. 2017; Lung et al. 2018). Dietze et al. (2017) reported that a rope-based oral fluid sampling method is equally adequate to detect CSFV RNA than the traditionally used oropharyngeal swabs sampling, which is more laborious and time-consuming. In addition, Petrini et al. (2017) reported that the probability of CSFV detection in oral fluids was identical or even higher than in blood samples.

11.3.4.3 Foot-and-Mouth-Disease and Swine Vesicular Disease

Lung et al. in a research published in 2018 reported an automated and integrated multiplex assay, including a multiplex microfluidic CARD (Chemistry and Reagent Devices) and a RT-PCR assay, able to successfully detect FMDV and swine vesicular disease virus in oral fluid from pigs. No FMD viral RNA was recovered from saliva in vaccinated pigs (Parida et al. 2007).

11.3.4.4 Influenza A

The Influenza A virus (IAV) subtypes H1N1, H1N2 and H3N2 cause explosive outbreaks of respiratory disease in swine. RT-PCR and virus isolation on nasal swab samples are currently the most used methods to detect IAV (Decorte et al. 2015). However, the biomarkers of the presence of IAV (nucleoprotein antibodies, RNA and/or DNA) have been detected in saliva and oral fluid specimens of infected pigs (Ramírez et al. 2012; Decorte et al. 2015, Biernacka et al. 2016; Gerber et al. 2017; Hernández-García et al. 2017).

11.3.4.5 Porcine Respiratory Disease Complex

Porcine respiratory disease complex (PRDC) is one of the most important diseases affecting pig production. Diseases related to PRDC lead to lung damage which could results in reduced feed efficiency, poor growth performance and higher medication and management costs (Fablet et al. 2012). Consequently, pig welfare is affected (Sørensen et al. 2006). Coinfection of several bacterial and viral pathogens are frequent in the PRDC, including *Actinobacillus pleuropneumoniae* (APP), *Pasteurella multocida* (PM), *Streptococcus suis* (SS), *Haemophilus parasuis* (HPS), *Mycoplasma hyopneumoniae* (MHP), *Mycoplasma hyorhinis* (MHR), Porcine reproductive and respiratory syndrome (PRRS) virus, porcine circovirus type 2 (PCV2), and swine influenza virus (SIV), and can be detected in saliva specimens (Cheong et al. 2017; González et al. 2017). PCV2, MHP, MHR and PM are detected most frequently among the PRDC affected swine (Hansen et al. 2010).

Pathogens affecting lung in swine have been traditionally detected in samples obtained through invasive and time-consuming procedures, such as blood, tissues or organs collected from slaughterhouses (Fablet et al. 2012). More recently studies have been proposed the used of oral fluids (OF) collected using cotton ropes as a suitable sample source for the detection, diagnosis, surveillance, and monitoring of various swine respiratory pathogens (Cheong et al. 2017).

PRRS antibodies and total antibodies have been detected in pig saliva (Langenhorst et al. 2012; Kittawornrat et al. 2013; Olsen et al. 2013; Ouyang et al. 2013; Decorte et al. 2014; Gerber et al. 2014; Kuiek et al. 2015; Sattler et al. 2015; Biernacka et al. 2016). DNA and/or specific immunoglobulins such as ApxIV-specific IgM, IgG and IgA can be detected in saliva of pigs with PRDC (Cheong

et al. 2017; González et al. 2017). PRRSV, PCV2, PM, HPS, APP, MHP, MHR, and SS were detected in the OF of asymptomatic pigs from Korean farms by real-time PCR, nested-PCR or PCR in a survey of porcine respiratory disease complex (Cheong et al. 2017). In this study, the majority of ropes arrived to the laboratory in good conditions, however, some ropes (5.3%) were not enough saturated with OF. As a consequence, these potential samples were discarded. While there are many advantages of OF analysis, such as reducing the number of samples required, labor intensity, costs, and time, some weakness could be observed. In the study performed by Cheong et al. (2017) it was reported that some depressed pigs or some pig that were not confident with the rope did not show interest in chewing the rope and, consequently, the rope was not saturated with OF and excluded from the study. In these cases, the rope may not represent the total population in the pen. However, results suggest that OF-bases analysis may be a potentially useful technique for individual monitoring of the major pathogens involved in PRDC.

11.3.4.6 Swine Erysipelas

Swine erysipelas is caused by the gram-positive facultative anaerobic bacterium *Erysipelothrix rhusiopathiae*. It is an important disease of pigs associated with mortality and poor growth performance due to skin disease (Opriessnig et al. 2011).

E. rhusiopathiae infection is diagnosed postmortem and the gold standard is the isolation of the bacteria from suspect lesions (Bender et al. 2009). However, detection of anti-*Erysipelothrix* IgM and IgG by ELISA and fluorescent microbead-based immunoassay (FMIA) and detection of *E. rhusiopathiae* DNA by real-time PCR in oral fluid from pigs experimentally infected have been used for diagnosis of swine erysipelas (Giménez-Lirola et al. 2013). Results from this study suggest that the use of oral fluid as a sample for detection of erysipelas could be useful in early outbreak detection.

11.4 Conclusions

Since the salivary antibody testing can be performed in a clinic or even at a home, rural and field settings, in some countries it is recommended and used for rapid screening of several infectious diseases (‘Global programme on AIDS. Recommendations for the selection and use of HIV antibody tests.’ 1992). If the screening test is positive, the person is referred to a health care provider for counselling and additional diagnostic blood tests. Because the test of saliva can be performed outside a formal hospital setting, and the collection of oral fluid is less invasive, less painful, less expensive (i.e., no trained personnel required), and safer, it becomes the sample of choice in community surveys requiring high community participation allowing serological testing on a broader front. As well as in humans, in veterinary medicine, the application of oral fluid-based tests also

facilitates monitoring, surveillance and diagnosis of infectious diseases in animal populations.

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