Point of care diagnostics and non-invasive sampling strategy: a review on major advances in veterinary diagnostics

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Abstract

The use of point of care diagnostics (POCD) in animal diseases has steadily increased over the years since its introduction. Its potential application to diagnose infectious diseases in remote and resource limited settings have made it an ideal diagnostic in animal disease diagnosis and surveillance. The rapid increase in incidence of emerging infectious diseases requires urgent attention where POCD could be indispensable tools for immediate detection and early warning of a potential pathogen. The advantages of being rapid, easily affordable and the ability to diagnose an infectious disease on spot has driven an intense effort to refine and build on the existing technologies to generate advanced POCD with incremental improvements in analytical performance to diagnose a broad spectrum of animal diseases. The rural communities in developing countries are invariably affected by the burden of infectious animal diseases due to limited access to diagnostics and animal health personnel. Besides, the alarming trend of emerging and transboundary diseases with pathogen spill-overs at livestock-wildlife interfaces has been identified as a threat to the domestic population and wildlife conservation. Under such circumstances, POCD coupled with non-invasive sampling techniques could be successfully deployed at field level without the use of sophisticated laboratory infrastructures. This review illustrates the current and prospective POCD for existing and emerging animal diseases, the status of non-invasive sampling strategies for animal diseases, and the tremendous potential of POCD to uplift the status of global animal health care.

Animal diseases, surveillance, field diagnosis, resource-limited settings

The incidence of emerging infectious diseases has increased in the recent decades and threatens to increase in the near future (Dikid et al. 2013). Pathogenic microorganisms have been expanding their population through evolutionary rescue by natural selection, a feature which is an interplay between co-evolutionary dynamics of hosts, pathogens, and environment (Gandon et al. 2013). The recurrent and widespread feature of evolutionary rescue of microorganisms emphasizes a broader term called 'emerging pathogens', which are increasing their fitness rapidly enough to prevent their extinction (Gandon et al. 2013). Besides genetic mutations and evolution of microorganisms, the major drivers of emerging diseases in human and animal populations can be human and environmental factors, such as (i) deforestation and associated biodiversity loss, (ii) imbalances in agricultural and food supply systems, (iii) increase in travel, trade, and traffic, (iv) persistence of poor health systems and protection practices and climate change (Engering et al. 2013). Since the 1940s, agricultural drivers were found to be associated with > 25% of all and > 50% of zoonotic infectious diseases that have emerged in humans through both wild and domestic animals (Rohr et al. 2019). Therefore, control and prevention of emerging and existing diseases of domestic and wildlife population is of paramount importance in order

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to avert the devastating effects on animal health and production, nutritional security and public health (McElwain and Thumbi 2017).

Animal health surveillance is an effective tool to monitor disease trends, for control measures and to provide data for use in risk analysis for animal and public health purposes (OIE 2019a). Therefore, epidemiology and laboratory networks play an important role in gathering data to understand disease dynamics and to provide an epidemiological interpretation of a defined disease (FAO 2011). Accuracy of disease diagnosis depends on the availability of an appropriate sample collected in a timely manner and transported under suitable conditions (Balogh et al. 2015). In most situations, maximum recovery of microbial pathogens is often not achieved due to inappropriate sample collection, transport and storage (Gilor and Gilor 2011). Collection and transportation of biological samples from animals is difficult especially in developing countries with limited resource settings as well as in regions where diagnostic laboratories are scarcely distributed. Besides, collecting biological samples from domestic, captive, and wild animals using invasive techniques requires skilled handler or restrainer which is not always feasible due to lack of skilled manpower (Zemanova 2019) or not allowed in wild fauna. In such situations, non-invasive techniques of sample collection and point-of-care diagnostics (POCD) are ideal components of animal disease diagnosis (Howson et al. 2017). Easy to use POCD format can be successfully deployed at field level and primary veterinary dispensaries without the use of sophisticated laboratory infrastructures. In this review, we will discuss the current status and future perspectives of POCD techniques in detection of animal diseases. Further, we will discuss the non-invasive sampling strategies in veterinary medicine and its importance in wildlife research.

Animal diseases of the past, present and future

We have all learnt about the importance of infectious diseases of animals, including rinderpest (cattle plague), the first animal disease to be eradicated globally in 2011. Eradication of rinderpest, the devastating disease of livestock responsible for world-wide famine and poverty was one of the greatest achievements in veterinary sciences (Roeder et al. 2013). With the establishment of Global Rinderpest Eradication Programme in 1994 by the World Organization for Animal Health (OIE) and Food and Agricultural Organization of the United Nations (FAO), the challenge of rinderpest eradication started with a time bound deadline established for its completion by the year 2010. The commercial production of the Plowright tissue culture rinderpest vaccine developed in 1960 (Plowright and Ferris 1962) and availability of effective diagnostics (indirect and competitive ELISA format) (Anderson et al. 1990) for detecting rinderpest antibodies to confirm diagnosis and monitor the effectiveness of vaccination programmes were the mainstay which led to the eradication of rinderpest (FAO 2012).

Since the eradication of rinderpest, the FAO and the OIE have been focusing on the global control of another devastating disease of small ruminants, peste-des-petits ruminants (PPR), with a goal of its eradication by the year 2030 (FAO and OIE 2015). Besides, keeping in view of the global economic consequences due to recent increase in epidemics of transboundary animal diseases such as foot and mouth disease (FMD) and African swine fever (ASF), the FAO and the OIE have launched global control strategies to implement the measures on preparedness, prevention, detection and control of both the diseases (FAO and OIE 2020). Among the OIE-listed livestock diseases, a sharp rise in the number of emerging diseases has been witnessed in the recent decade. Some of the examples include lumpy skin disease (LSD) (Tasioudi et al. 2016; Sudhakar et al. 2020), Rift Valley fever (RVF) (Gaudreault et al. 2019; Lagare et al. 2019), porcine reproductive and respiratory syndrome (PRRS) (Rajkhowa et al. 2015; Zhang et al. 2019), camel pox infections

(Al-Zi'abi et al. 2007; Erster et al. 2018) and equine coronavirus infections (Pusterla et al. 2016; Nemoto et al. 2019). Several other diseases of livestock that have re-emerged in the recent years due to the changing incidence of pathogens and patterns of diseases over time include blue tongue (BT) (Purse et al. 2005; Sailleau et al. 2017), African horse sickness (AHS) (Maclachlan and Guthrie 2010; Thompson et al. 2012), West Nile fever (WNF) (Schvartz et al. 2020) and anthrax (Kisaakye et al. 2018; Stella et al. 2020). Bearing in mind the recent patterns of evolving novel pathogens and emerging diseases such as influenza, Nipah, Middle East respiratory syndrome (MERS) and most recently coronavirus disease (COVID-19) in animals, constant awareness and pursuance of effective strategies for controlling infectious diseases and disease emergence thus remain crucial. The unpredictable nature of evolving pathogens requires immediate attention from clinical microbiologist and infectious disease experts to stimulate research on emerging infections including surveillance and diagnostics.

Progress in animal disease surveillance by use of POCD

The development of simple, rapid, and portable diagnostic devices is now considered a priority for animal diseases. In the recent years, tremendous advances in POCD have been witnessed, which are a result of continuous developments in biosensors, microfluidic, bioanalytical platforms, assay formats, lab-on-a-chip technologies and complementary technologies (Vashist 2017). This section describes the current status of POCD focusing on antigen/antibody and nucleic acid detection technologies for on-spot detection of animal diseases and their future utilization as complementary to conventional laboratory techniques.

Antigen/antibody detection systems

Lateral flow device (LFD)

Detection of antigens can be done using portable immunochromatographic strips, also known as antigen-lateral flow device (Ag-LFD), which works by binding both antigen and antibody-coated detector particles to bands of capturing monoclonal antibody (mAb) on various zones of a polymeric strip through capillary action (Howson et al. 2017). The lateral flow technology was derived from latex agglutination test developed by Singer and Plotz in 1956 (Singer and Plotz 1956). A lateral flow test strip consists of four overlapping membranes, sample pad, conjugate pad, nitrocellulose membrane and absorbent pad (Sharma et al. 2015). The typical configuration of an immunochromatographic strip and its mechanism of action are illustrated in Fig. 1 (Plate III). As shown in the figure, the sample containing the target antigen/analyte or biomarker is applied on the sample pad, which is impregnated with buffer salts and surfactants that make the sample suitable for interaction with the detection system. The treated sample migrates through the conjugate pad**,** which contains antibodies specific to the target agent and are conjugated to coloured or fluorescent particles (colloidal gold/latex microspheres/carbon nanotubes) (Koczula and Gallotta 2016). The conjugated antibody bound to the target antigen migrates along the strip into the detection zone which is a porous membrane usually composed of nitrocellulose, where the antigen-conjugated antibody complex is trapped by the immobilized capture antibody in the test line forming a coloured reaction indicating the presence of the antigen of interest. The excess conjugated antibody will be captured at the control zone by secondary antibody which is indicative of proper flow of the sample through the strip (Sajid et al. 2015; Koczula and Gallotta 2016). The absorbent pad maintains the flow rate of the buffer over the membrane and stops back flow of the sample. LFD is available in three formats, (i) sandwich, (ii) competitive, and (iii) multiplex detection format (Sajid

et al. 2015). LFDs are rapid (display results within 5–30 min), user-friendly, inexpensive and disposable which makes them an ideal device of disease detection under low resource settings (Koczula and Gallotta 2016). Since its introduction, the technology and its applications have been used in several human diseases (Sharma et al. 2015). The OIE have now recommended the use of LFD for rapid detection of high impact livestock diseases such as FMD (OIE 2019b) and PPR (OIE 2019c). A comprehensive list of Ag-LFDs developed for detection of OIE listed diseases have been tabulated (Table 1). In addition, with the developments in reader technology and advancements in raw materials, such as labels, LFD can match the sensitivity of enzyme linked immunosorbent assay (ELISA), and might be a substitute to ELISA in sero-epidemiology of animal diseases in near future.

Table 1. Overview of antigen-LFDs developed for detection of OIE listed livestock diseases.

Animal disease	Agent	mAb target against (Protein/Whole purified antigen)	References
Foot-and-mouth disease	FMDV	FMDV type SAT 2 whole viral antigen	Oem et al. 2009
		FMDV types O, A, C, and Asia 1 whole viral antigen	Ferris et al. 2010
Peste-des-petits- ruminants	PPRV	PPRV-Haemagglutinin protein	Baron et al. 2014
African swine fever	ASFV	ASFV-VP 72 protein	Sastre et al. 2016
Classical swine fever	CSFV	CSFV-whole viral antigen	Sambandam et al. 2017
Vesicular stomatitis	VSV	VSV-glycoprotein: Indiana (subtype 1) and New Jersey	Ferris et al. 2012
Bovine viral diarrhoea	BVDV	BVDV-Erns protein	IDEXX Laboratories, Inc., Westbrook, Maine, USA
Bovine tuberculosis	*M. bovis*	Irradiated *M. bovis* AF2122/97	Stewart et al. 2017
Anthrax	*B. anthracis*	*B. anthracis* capsular polypeptide (Polyglutamic acid)	Kolton et al. 2019
Rift Valley fever	RVFV	RVFV-Nucleoprotein	Cêtre-Sossah et al. 2019
West Nile fever	WNV	WNV-Envelope glycoprotein	Rebollo et al. 2018
Rabies	RABV	RABV-Nucleoprotein	Kang et al. 2007

mAb - monoclonal antibody; FMDV - *Foot-and-mouth disease virus*; PPRV - *Peste-des-petits-ruminants virus*; ASFV - *African swine fever virus*; CSFV - *Classical swine fever virus*; VSV - *Vesicular stomatitis virus*; BVDV - *Bovine viral diarrhoea virus*; PRRSV - *Porcine reproductive and respiratory syndrome virus*; *M. bovis* - *Mycobacterium bovis*; *B. anthracis* - *Bacillus anthracis*; RVFV - *Rift Valley fever virus*; WNF - *West Nile fever virus*; RABV - *Rabies virus*

Dipstick assay

The dipstick assay is a rapid immunochromatographic assay, which is a simplified version of LFD. In dipstick assay, the sample pad and the conjugate pad are substituted by a solution into which the nitrocellulose membrane is immersed (de Puig et al. 2017). The nitrocellulose strip bearing immobilized antibodies is put in contact with a solution containing the running buffer, biological sample and antibody conjugated to coloured or fluorescent particles, mostly colloidal gold (Plate III, Fig. 2). Dipstick assay eliminates the need to dry down the conjugated antibody. Dipstick assay is now gaining popularity as POCD as it is applicable in almost every environment from field to clinical settings. The dipstick technology has been developed to detect different animal diseases such as canine leishmaniasis (Schallig et al. 2004), bovine tuberculosis (Mosaad et al. 2012), and bovine brucellosis (Poonati et al. 2020).

Immunocomb assay

The immunocomb assay is a highly sensitive simplified form of ELISA which can be described as an enzyme labelled ‘dot assay’ that detects antibody levels in serum or

whole blood. The immunocomb assay is available in a kit format with all the necessary reagents to develop the test without the need of sophisticated equipment for classic ELISA like special dispensers, automatic washer or electronic reader. Immunocomb kits contain two main components: a comb shaped plastic card, referred to as the comb and a multi compartment developing plate (Plate IV, Fig. 3). Each comb has 12 teeth, activated with specific antigens localized to dots on the comb, which may be used individually or any number up to 10, by breaking off the desired number of teeth from the comb and using the corresponding column of wells in the developing plate (Biogal Galed Labs 2015). The assay can be performed at room temperature (20–25 °C) within a simple clinical setting or veterinary dispensary and provides results within 20–60 min. The reaction time may vary according to antigens and antigen/antibody reactions. The level of antibodies (antibody titres to a particular antigen) is determined according to the intensity of the test colour developed which can be interpreted by naked eye or with a comb scale provided with the kit. Commercial immunocomb assay kits are currently available for detection of bovine (brucellosis and leptospirosis), canine (parvovirus infections, canine distemper, brucellosis, ehrlichiosis and leptospirosis) and feline diseases (feline infectious peritonitis).

Nucleic acid-based detection systems

Recombinase polymerase amplification-lateral flow dipstick (RPA-LFD) assay

Recombinase polymerase amplification (RPA) is a highly sensitive and selective isothermal amplification technique that can operate at 37–42 °C with minimal sample preparation and has been used to amplify RNAs, miRNA, ssDNA and dsDNA from a wide variety of organisms (Lobato and O'Sullivan 2018). To address the requirements of amplification for use in low-resource settings, RPA is remarkable due to its simplicity, high sensitivity, selectivity and rapid amplification (results in 5–20 min), making it an affordable user-friendly POC device (Lobato and O'Sullivan 2018). The RPA technology was first developed in 2006 by Piepenburg et al. (2006) and is currently commercialised under the license of TwistDx Limited. The mechanism of RPA relies on a synthetically engineered adaptation of a natural cellular process called homologous recombination (a key process in DNA metabolism). The standard RPA reaction reagents comprise three key proteins, (i) recombinase, (ii) recombinase loading factor, and (iii) single-stranded binding protein, which subsequently coordinate with additional components such as dNTPs, DNA polymerase, ATP, crowding agents (polyethyleneglycol) and salt molecules to perform the reaction (Li et al. 2020). The RPA process starts with binding of the recombinase protein to the primers assisted by the recombinase loading factor in presence of ATP and the crowding agent, forming the recombinase-primer complex (Lobato and Sullivan 2018). The complex then searches for their homologous sequences in the duplex DNA and invades the duplex DNA forming a D-loop structure. The side of the D-loop that remains single-stranded is stabilized by the single-stranded binding protein (Li et al. 2020). The recombinase then disassembles and a strand displacing DNA polymerase binds to the primer to elongate it in the presence of dNTPs. As the polymerisation continues, the two parental strands continue to separate, ultimately resulting in the exponential accumulation of amplified duplex DNA (Moore and Jaykus 2017). The amplified product can be detected by LFD assay, and the process is combinedly known as RPA-LFD. Multiple other techniques can also be used for RPA amplification product detection including agarose gel electrophoresis and real-time fluorescent detection (Tu et al. 2018).

In the recent years, a number of RPA-LFD assays have been developed for diagnosis of infectious animal diseases. RPA assays combined with a real-time fluorescent detection (real-time RPA assay) and lateral flow dipstick (RPA LFD assay) have been developed for rapid detection of goatpox virus and sheeppox virus (Yang et al. 2017a). RPA-LFD

assay as an alternative to conventional ELISA for the screening of *Bovine leukaemia virus* (BLV) both at laboratory and field application has been recommended in a recent study (Tu et al. 2018). Detection of the H9-subtype of *Avian influenza virus* by RPA LFD assay with 10 × more sensitivity than conventional RT-PCR has also been documented (Wang et al. 2019). Several other significant animal diseases for which RPA-LFD assays have been developed include detection of *Porcine circovirus type 2* (PCV-2) (Yang et al. 2017b), PPRV (Yang et al. 2017c), ASFV (Miao et al. 2019), *Porcine deltacoronavirus* (PDCoV) (Gao et al. 2020), *Pasteurella multocida* (Zhao et al. 2019), *Bovine viral diarrhoea virus* (BVDV) (Hou et al. 2018a), *Bovine ephemeral fever virus* (BEFV) (Hou et al. 2018b), *Mycoplasma bovis* (Zhao et al. 2018), *Infectious bovine rhinotracheitis virus* (IBRV) (Hou et al. 2017), FMDV (Wang et al. 2018b), *Brucella* species (Qin et al. 2019), PRRSV (Wang et al. 2017) and LSDV (Shalaby et al. 2016). The use of RPA-LFD assay in diagnostic application is therefore becoming a molecular tool of choice for the rapid, specific, and cost-effective approach for identification of animal diseases in laboratory settings as well as in field conditions.

Loop-mediated isothermal amplification

Loop-mediated isothermal amplification (LAMP) is an established isothermal nucleic acid amplification method developed in the year 2000 by Notomi et al. (2000). LAMP has gained a significant interest among researchers and industries because of its high specificity, efficiency, and rapidity. The LAMP reaction can be completed in a water bath or heat block with an optimum temperature range between 60–65 °C (Venkatesan et al. 2020). The assay uses four specially designed primers capable of recognizing six different regions in the target DNA, making the process highly specific (Venkatesan et al. 2020). However, the currently improved LAMP assays employ a total of six primers, recognising eight distinct sites of the target sequence (Nagamine et al. 2002), making the specificity of the assay extremely high.

The LAMP assay relies on auto-cycling strand displacement DNA synthesis, performed by a DNA polymerase with high strand displacement activity and a set of two specially designed inner and two outer primers (Notomi et al. 2000). The assay initially utilizes the inner forward primer containing two target sequences specific to two different regions in the template DNA and starts complementary strand synthesis (Silva et al. 2020). The outer primers then hybridize the sequence in the target DNA releasing a single-stranded DNA. The single-stranded DNA then serves as a template for DNA synthesis primed by the second inner and outer primers that hybridize to the other end of the target, producing a stem loop DNA (Notomi et al. 2000). In the subsequent process, one inner primer hybridizes to the loop on the product and initiates displacement DNA synthesis, yielding the original stem loop and a new stem loop, and the cycling reaction continues (Notomi et al. 2000). For the amplification of RNA viruses, a reverse transcription step is undertaken prior to the LAMP reaction.

Several LAMP assays have been developed in the recent years for detection of animal diseases in field and resource-limited settings. A comprehensive list of LAMP techniques developed for diagnosis of important animal diseases has been tabulated (Table 2).

Linear-after-the-exponential polymerase chain reaction

Linear-after-the-exponential polymerase chain reaction (LATE-PCR), first described by Sanchez et al. (2004) is a novel approach to asymmetric PCR. LATE-PCR can utilize as few as a single DNA/RNA molecule and primers are designed with adjusted melting temperatures to increase the amplification efficiency (Pierce et al. 2010). The standard reaction process of LATE-PCR consists of a limiting primer, excess primer and a molecular beacon (mismatch-tolerant probe)

Table 2. Loop-mediated isothermal amplification (LAMP) assay developed for existing and emerging animal diseases.

Animal disease	Target genes/organisms	References
Anthrax	*B. anthracis* pag gene (encoding protective antigen portion of anthrax toxin)	Upadhyay et al. 2020
	B. anthracis spores	Jain et al. 2011
Blue tongue	BTV genome segment 1	Maan et al. 2016
Bovine brucellosis	Conserved BruAb2 0168 region of *B. abortus*	Karthik et al. 2014; Kang et al. 2015
Foot-and-mouth disease	FMDV 2B	Chen et al. 2011
	FMDV-3D pol	Farooq et al. 2015
Haemorrhagic septicaemia	*P. multocida* KMT1 gene	Sun et al. 2010; Bhimani et al. 2015
Capripox virus infections (LSD and goat pox)	CaPV-VP39 gene and P32 gene	Mwanandota et al. 2018
Camelpox virus infections	CMLV-C18L gene	Venkatesan et al. 2012
Peste-des-petits-ruminants	PPRV-Nucleocapsid gene	Mahapatra et al. 2019; Rajko-Nenow et al. 2019
African swine fever	ASFV-VP73 gene, putative DNA primase and Topoisomerase II genes	James et al. 2010
Classical swine fever	CSFV 5′ NTR	Chowdry et al. 2014
	CSFV NS5B gene and 5′ NTR	Postel et al. 2015
Rabies	RABV-Nucleoprotein gene	Saitou et al. 2010
Vesicular stomatitis	VSV-Spanning nucleotides 1376–1598 (junction between nucleocapsid and phosphoprotein)	Fowler et al. 2016
Bovine viral diarrhoea	BVDV- 5′UTR	Fan et al. 2012
Bovine tuberculosis	*M. bovis* cell surface lipoprotein mpt83	Zhang et al. 2011
Rift Valley fever	RVFV S RNA segment	Han et al. 2020
West Nile fever	WNFV Envelope gene	Parida et al. 2004
Porcine reproductive and respiratory syndrome	PRRSV-ORF6	Li et al. 2009
	PRRSV-Nucleocapsid gene	Park et al. 2016
Porcine circovirus 2 infections	PCV-2 Capsid (cap) gene	Chen et al. 2008
Porcine circovirus 3 infections	PCV-3 ORF2	Zheng et al. 2018
	PCV-3 cap gene	Park et al. 2018
Porcine epidemic diarrhoea	PEDV Membrane gene	Yu et al. 2015
Novel swine acute diarrhoea syndrome coronavirus	SADS-CoV Nucleocapsid gene	Wang et al. 2018a
Porcine deltacoronavirus infections	PDCoV Nucleocapsid gene	Zhang et al. 2017
Porcine pegivirus infections	PPgV NS5A gene	Li et al. 2019
Japanese encephalitis virus infection	JEV Envelope gene	Liu et al. 2012
Contagious ecthyma	Orf virus-B2L gene	Venkatesan et al. 2016
	Orf virus F1L gene	Wang et al. 2015

B. anthracis - *Bacillus anthracis*; BTV - *Blue tongue virus*; *B. abortus* - *Brucella abortus*; FMDV - *Foot-and-mouth disease virus*; *P. multocida* - *Pasteurella multocida*; CaPV - *Capripox virus*; CMLV - *Camelpox virus*; PPRV - *Peste-des-petits-ruminants virus*; ASFV - *African swine fever virus*; CSFV - *Classical swine fever virus*; RABV - *Rabies virus*; VSV - *Vesicular stomatitis virus*; BVDV - *Bovine viral diarrhoea virus*; *M. bovis* - *Mycobacterium bovis*; RVFV - *Rift Valley fever virus*; WNF - *West Nile fever virus*; PRRSV - *Porcine reproductive and respiratory syndrome virus*; PCV-2 - *Porcine circovirus 2*; PCV-3 - *Porcine circovirus 3*; PEDV - *Porcine epidemic diarrhoea virus*; SADS-CoV - *Swine acute diarrhoea syndrome coronavirus*; PDCoV - *Porcine deltacoronavirus*; PPgV - *Porcine pegivirus*; JEV - *Japanese encephalitis virus*

(Johann et al. 2015). LATE-PCR begins with an exponential phase in which amplification efficiency is similar to that of conventional symmetric PCR. Once the limiting primer is depleted, the reaction abruptly switches to linear amplification, and the single-stranded product is made for many additional thermal cycles. The accumulating single-stranded products will have no complementary strands and are therefore will be free to hybridize to the probe emitting fluorescent signals (Pierce et al. 2005). The most known application of LATE PCR is in FMDV serotyping, in which the field strains with novel sequence mutations can be detected through fluorescent signals (Pierce et al. 2010).

Future diagnostic models

Microfluidics

Microfluidics is an emerging technology of the recent years because of its significant application in the field of chemistry, biology, medicine, and physical sciences (Bragheri et al. 2020). The microfluidic technology involves the manipulation of small volumes of fluids, typically in nano or microlitres (10^{-9}–10^{-6} l) within networks of channels that have dimensions of tens to hundreds of micrometres (Busin et al. 2016). The concept of microfluidics constitutes the basis of integrated systems known as micro total analysis systems or lab-on-a-chip (LOC), which means the part of the chip acts as a part of the lab (Zhang and Hoshino 2018). The LOC device comprises of integrated microsystems embedded inside the chip (usually made of silicon or glass) such as microchannels, filters, pumps, valves and mixers which can be designed as a diagnostic assay (Shirzadfar and Khanahmadi 2018) and can be applied to steamline the complex assay protocols of detecting infectious diseases. However, there has been a very limited application of this technology in the veterinary field to date (Busin et al. 2016). Such fully automated microfluidic platform has been developed only recently, for multiplex detection of high threat livestock diseases such as FMD, classical swine fever (CSF) and vesicular stomatitis (VS) (Lung et al. 2019). Another feature of microfluidic technology includes microfluidic paper-based analytical devices (Busin et al. 2016). A recent application of microfluidic paper-based devices has been developed for detection of *Bovine herpesvirus 1* (BoHV-1), *Brucella* and *Leptospira* species (Yang et al. 2018). A hybrid paper-based microfluidic platform compatible with 96-well microplates has been recently developed for rapid and low-cost translation and optimization of laboratory-based ELISA assay into paper ELISA (Busin et al. 2018).

Biosensors

Recent advances in biosensor technologies have the potential to match or surpass the conventional diagnostics with respect to sensitivity, selectivity, accuracy and cost (Du and Zhou 2018). A biosensor is an integrated receptor-transducer device that uses a biological recognition element to provide selective, quantitative or semi-quantitative information. Most biosensor technology relating to disease-related detection employ a transducer that converts a biological recognition event into a detectable signal (electrochemical, optical or piezoelectric) and displays the presence, concentration, or reaction process of the target biomarker in the analyte (Du and Zhou 2018). Modern sensor technologies such as fluorescence resonance energy transfer and quantum dots (Zhang et al. 2015) have been developed for rapid and sensitive detection of several animal pathogens such as PRRSV, FMDV, BHV-1 and BVDV (Neethirajan et al. 2017). Novel diagnostic approach based on biosensing and photonic technologies have been developed for detection of emerging and endemic viruses which include ASFV, PRRSV, *Swine influenza A virus* (SIV), *Porcine parvovirus* (PPV), PCV-2 and CSFV (Montagnese et al. 2019). Another cutting-edge

sensor technology is based on surface plasmon resonance (SPR) (Neethirajan 2017). The SPR sensors provide sensitive, label-free and real-time monitoring of reactions and can quantify the characteristics of biomolecular (e.g., oligonucleotides, proteins, viruses, bacteria etc.) interactions on a surface, including their kinetics, affinity and concentration (Skottrup et al. 2008). In recent years, SPR biosensors have been used to detect avian influenza A viruses: H5N1 (Bai et al. 2012) and H7N9 (Chang et al. 2018), SIV: H1N1 (Yoo et al. 2020), CSF (Mustafa et al. 2014), PCV-2 (Hu et al. 2014), *Leptospira* species (Raikwar et al. 2020) and *Brucella abortus* (Gupta et al. 2011).

Current status of non-invasive sampling strategies

Non-invasive samples for diagnostic purposes have been increasingly used in different scientific studies. They consist of sampling techniques that do not require penetration of the skin or a mucosal barrier to obtain biological samples (Baneth 2015). The non-invasive samples include conjunctival, nasal and oral mucosal swabs, milk, oral fluids/saliva, hair, urine and faeces (Baneth 2015; Mengüllüoğlu et al. 2019). This technique has now become an alternative to invasive sampling methods (venous blood collection/aspirations of lymph nodes or the bone marrow) and has been widely used by biologists in wildlife research (Dib et al. 2019). Because of the obvious advantage of being relatively simple to employ and standardize, non-invasive sampling strategies hold great promise for studies that cover large areas to investigate diseases in free-ranging animals and atypical hosts that are logistically difficult and time consuming to capture and manipulate (Kelly et al. 2012). In the last two decades, various user-friendly techniques for collection and transport of non-invasive samples (oral fluids and swabs in particular) have been developed to be used in biomedical research (Segal and Wong 2008). Such innovative non-invasive techniques of sample collection can also be used for detection and surveillance of animal diseases. Research on animal diseases has demonstrated the potential of non-invasive samples for accurate diagnosis of livestock diseases, a number of which have been described:

Oral fluids/saliva

The use of oral fluids/saliva as a diagnostic fluid is a broadening perspective in clinical animal disease diagnosis and monitoring (Prickett and Zimmerman 2010). Saliva offers a source of locally produced and serum derived markers with non-invasive animal practices (Gutiérrez et al. 2017). Oral fluids serve as an efficient sample for detection of animal pathogens that might originate in affected tissues associated with the buccal cavity or reach the buccal cavity from the circulatory system via the oral mucosal transudate (OMT) (Prickett 2009). Saliva comprises primarily of secretory IgA (sIgA), whereas OMT contains a mixture of sIgA, IgG and IgM, thus, provides a richer source of antibodies, including those directed against bacterial and viral pathogens (Corstjens et al. 2012). Detection of antigens in oral fluids have been confirmed in several animal diseases following natural as well as experimental infections such as PRRS and PCV-2 infections (Prickett 2009), Johne's disease (Sorge et al. 2013), FMD (Senthilkumaran et al. 2017), bovine papular stomatitis (Eirai et al. 2016), CSF (Beemer et al. 2019), ASF (Beemer et al. 2019) and PPR (Parida et al. 2019). Bearing in mind the animal diseases with a diverse host range such as PPR, ASF, FMD, rabies, canine distemper and coronavirus infections, oral fluid-based surveillance of pathogens, as a non-invasive and safe source, would be an efficient approach in diagnosis of animal diseases in domestic as well as in wildlife. More recently, rope-based oral fluid sampling has gained substantial importance in transboundary animal diseases for which effective population level sampling methods have not been available. Rope-in-a-bait based oral fluid sampling technique has been tested and found to be effective in early detection of FMDV infections of wild boars

(Mouchantat et al. 2014a), CSF infections in wild boars (Mouchantat et al. 2014b) and domestic pigs (Dietze et al. 2016), and detection of ASFV in wild boars (Männistö 2018).

Swabs

Swabs (nasal, naso/oro-pharyngeal), as non-invasive samples, could be an excellent source of potential respiratory pathogens. The current example is detection of pandemic COVID-19 infections in humans as well as animals using naso pharyngeal swabs (Sit et al. 2020; Segalés et al. 2020). Research on infectious animal disease detection have proved that detection of viruses can be accurately received in molecular tests, isolation as well as in serology through use of nasal swabs (Dynon et al. 2007). Nasal swabs have proved to be suitable for FMDV detection by RT-PCR even during the asymptomatic stages of infection (Marquardt et al. 1995). Nasal swabs have shown to be effective in detection of other respiratory pathogens like BHV-1, *Bovine parainfluenza 3 virus* (BPI3V) (Gangil et al. 2020), *Mycoplasma hyopneumoniae* (Otagiri et al. 2005), *Mycoplasma bovis* and *Mannheimia haemolytica* (Godinho et al. 2007).

Faecal samples

Faecal samples as non-invasive samples have become a regular choice in wildlife biology, population monitoring and ecological research globally. Advantages of faecal sample-based wildlife research include easy collection, access to large sample sizes and spatio-temporal coverage (Biswas et al. 2019). Such faecal sampling protocol could be used for detection of infectious diseases in herbivores (elephants and other wild ungulates) as well as in carnivores. *Elephant endotheliotropic herpes virus* (EEHV) infection is a highly fatal disease in young Asian elephants. The virus is ubiquitous in elephants. The samples that are used regularly for diagnosis of the infection are trunk washings, blood, and oral swabs. But these samples are difficult to obtain from elephants in the wild as the technique is invasive. The non-invasive technique of sampling is highly essential in such instances. The non-invasive sampling for EEHV was done by collecting chewed plant and faeces (Jeffrey et al. 2020). Bataille et al. (2019), concluded in their study on PPR that faecal samples can be collected non-invasively from the artiodactyls which can be used for surveillance and control of the disease.

Bioaerosol sampling

Bioaerosol or aerosol sampling is a novel concept of non-invasive approach which can be used for detection of emerging viruses, mostly of respiratory origin. In the recent decade, emerging zoonotic viruses like *Severe acute respiratory syndrome coronavirus* (SARS CoV), MERS-CoV, avian strains of IAV (eg, H5N1, H7N9, and H9N2), and most recently the SARS-CoV-2 pandemics have led to considerable mortality and morbidity in humans and animals (Wang et al. 2020; Oreshkova et al. 2020). High population density, international tourism and trade traffic have fuelled the risk of novel emerging respiratory epidemics. With the approach of bioaerosol sampling, such biological threats can be quickly identified and robustly tracked to initiate an early emergency response to novel pathogens (Coleman et al. 2018).

Bioaerosol sampling devices works by extracting a representative bioaerosol sample from an air environment and then preserving the bioaerosol sample properties needed for sample analysis by traditional and modern analysis techniques (Mainelis 2020). Various bioaerosol samplers have been developed that include (i) filtration and filter-based samplers, (ii) impaction-based samplers, (iii) agar-based samplers (iv), liquid-based samplers, and (v) electrostatic collection of micro-organisms (Mainelis 2020). In response to the spread of zoonotic infectious disease through air, bioaerosol sampling techniques have been

adapted for (i) influenza virus detection in live animal markets (Zhou et al. 2016; Wang et al. 2020), swine production facilities (Poh et al. 2017), mass rapid transit networks (Coleman et al. 2018) as well as in airport settings (Bailey et al. 2018). Bio-aerosol sampling has an advantage as a non-invasive sampling approach since it is accepted by animal vendors at live markets as well as in production facilities. Therefore, bioaerosol sampling can be an effective screening tool for emerging and novel viruses which can be followed up with traditional method of swabbing if evidence of a novel virus is found (Wang et al. 2020).

Conclusion

The status of global animal disease epidemiology is complicated by threats of both existing and emerging infectious diseases. These challenges highlight the need for rapid and specific diagnosis, coupled with timely initiation of appropriate treatment in order to prevent and control the spread of infectious or zoonotic diseases, thereby protecting human health and safety. During the last decade, point of care diagnostics have gained their impact in several fields such as infectious disease diagnosis, animal health management and animal reproduction. POCDs such as Ag-LFDs, RPA-LFD and LAMP have been extensively researched and developed considering their obvious advantages over traditional laboratory-based diagnostics which usually involves laborious and expensive laboratory techniques and dedicated technical personnel. In addition, non-invasive approach of sample collection coupled with a point-of-care test can be of particular importance in diagnosis of economically important and emerging animal pathogens of domestic and wildlife in field-based settings. While economic benefits of POCDs and better outcomes with respect to the conventional diagnostics are still discussed, it is likely that these tests will gain further importance in veterinary medicine in near future with decreasing processing costs and improved robustness.

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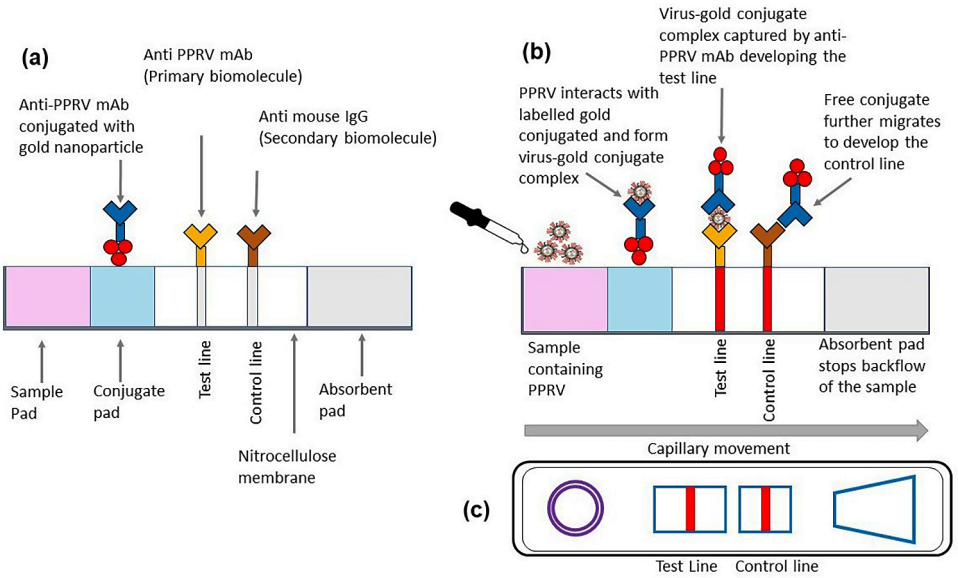

Fig. 1. (a) Schematic representation of a sandwich immunochromatographic or antigen-lateral flow assay citing *Peste-des-petits ruminants virus* (PPRV) as an example. (b) Sample containing PPRV is added to the sample pad and flows to the conjugate pad where it combines with anti PPRV mAb conjugated with gold nanoparticle and forms virus-conjugate complex. The complex is carried by capillary flow along the nitrocellulose membrane to the test line, where the virus become sandwiched between labelled conjugate and primary antibody (anti-PPRV mAb) forming conjugate-virus-primary antibody complex forming a reddish-purple line on the test line indicating the presence of PPRV. The remaining conjugates are carried further along the strip until they come to the control line, where they are bound by secondary antibody (anti-mouse IgG) creating another colour reaction indicative of proper liquid flow through the strip. Negative results are indicated by a single-coloured band in the control line (c) Representation of an immunochromatographic strip inside a plastic cassette.

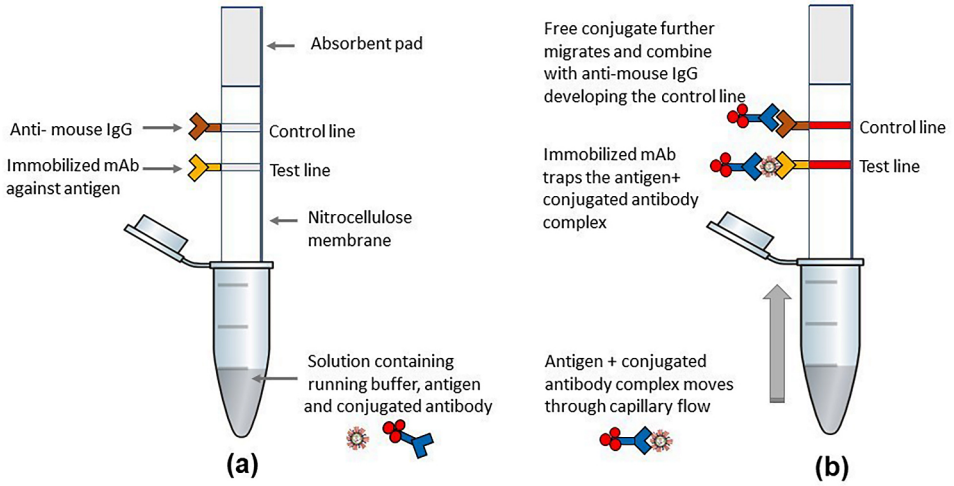

Fig 2. Basic structure of dipstick assay. (a) A dipstick placed into an Eppendorf tube containing running buffer, sample, and conjugated antibody. (b) Antigen specific to conjugated antibody combines and the complex wicks through a nitrocellulose strip which has immobilized antibodies mAb that capture the complex, providing the readout.

Plate IV

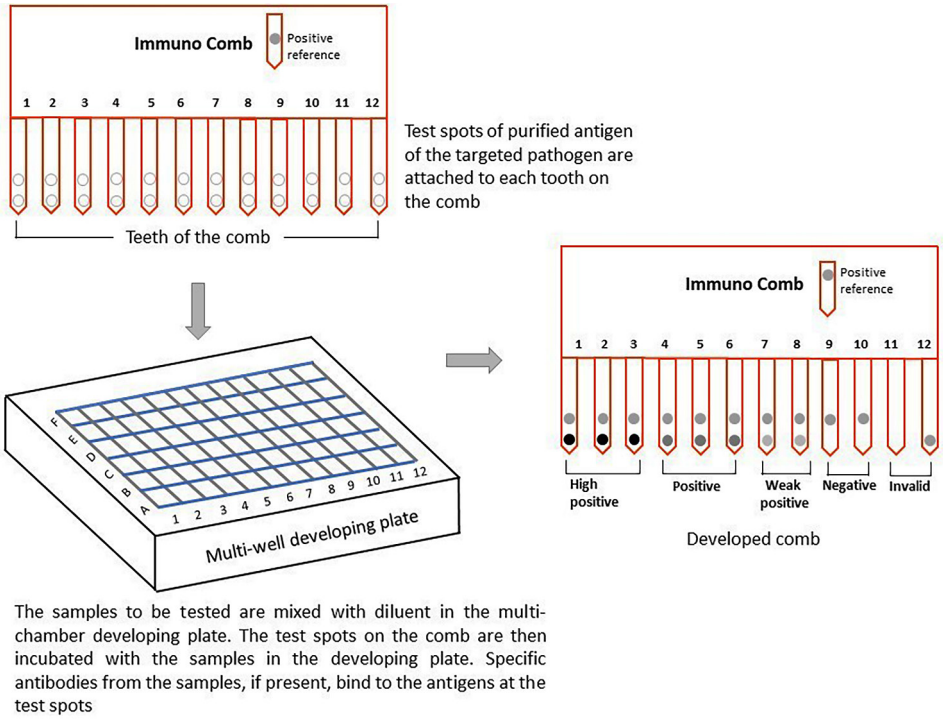

Fig 3. Schematic representation of immunocomb assay for detection of antibodies specific to targeted antigen.