ISSN 1466-2523

Animal Health Research Reviews **19**(1); 53–64
doi:10.1017/S1466252318000038

Review

Herd-level infectious disease surveillance of livestock populations using aggregate samples

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Received 8 December 2017; Accepted 5 April 2018;
First published online 21 May 2018

Abstract

All sectors of livestock production are in the process of shifting from small populations on many farms to large populations on fewer farms. A concurrent shift has occurred in the number of livestock moved across political boundaries. The unintended consequence of these changes has been the appearance of multifactorial diseases that are resistant to traditional methods of prevention and control. The need to understand complex animal health conditions mandates a shift toward the collection of longitudinal animal health data. Historically, collection of such data has frustrated and challenged animal health specialists. A promising trend in the evolution toward more efficient and effective livestock disease surveillance is the increased use of aggregate samples, e.g. bulk tank milk and oral fluid specimens. These sample types provide the means to monitor disease, estimate herd prevalence, and evaluate spatiotemporal trends in disease distribution. Thus, this article provides an overview of the use of bulk tank milk and pen-based oral fluids in the surveillance of livestock populations for infectious diseases.

Keywords: Aggregate sample, bulk tank milk, oral fluid, surveillance.

Introduction

Globally and locally, achieving the control of historically impactful infectious diseases of livestock continues to frustrate producers and challenge animal health specialists. A core requirement of a successful control program is the ongoing collection of disease data from populations. Schwabe (1982) describes this as the process of establishing baseline levels 'against which effects of intervention (control) efforts can be measured'.

The ongoing burden of disease in endemic areas and the expansion of infectious agents into previously free areas expose the frailty of current surveillance and response/control programs (Backer *et al.*, 2009; Lee, 2015; Saeed *et al.*, 2015; Neira *et al.*, 2017). Foot-and-mouth disease virus (FMDV) was identified in 1897, but 116 years later, endemic FMDV losses were estimated at $6.5–$21 billion dollars annually and only 66 of the 181 (36.5%) OIE-member countries are 'FMD free where vaccination is not practiced' (Longjam *et al.*, 2011; Knight-Jones and Rushton, 2013; OIE, 2017*a*). Classical swine fever virus (CSFV) was identified in 1903 (de Schweinitz, Dorset, 1903), but in 2017, just 32 of the 181 (17.7%) OIE-member countries are considered free of CSFV (OIE, 2017*b*). This, despite the profound global economic burden of CSFV and the clear benefits of eradication, e.g. the benefit:cost ratio of CSFV eradication in the USA was estimated at ≥13.2 (USDA, 1981; Pinto *et al.*, 2011). Initially identified on the basis of outbreaks of unknown origin in the 1980s, porcine reproductive and respiratory syndrome virus (PRRSV) was isolated in 1991 and has become endemic in most major pork-producing regions of the world (Wensvoort *et al.*, 1991; Zimmerman *et al.*, 2012). Holtkamp *et al.* (2013) estimated the US pork producers' losses to PRRSV at $664 million annually. Nathues *et al.* (2017) estimated losses to European producers at €126.79 per sow per year and €3.77 per pig marketed in herds with 'slight' PRRS.

A promising trend in the evolution toward more efficient and effective livestock disease surveillance is the increased use of aggregate samples (Thurmond and Perez, 2006; Strutzberg-Minder *et al.*, 2015; Gibert *et al.*, 2017; Rotolo, *et al.*, 2017). By definition, an aggregate sample represents two or more animals at a specific location and time, e.g. bulk tank milk and pen-based oral fluid samples.

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Table 1. Pathogens detected in bulk tank milk

Method	Reference
Nucleic acid detection	
Border disease virus	Berriatua *et al.* (2006)
Bovine viral diarrhea virus	Drew *et al.* (1999); Houe (1999); Kramps *et al.* (1999); Lanyon *et al.* (2014); Radwan *et al.* (1995); Renshaw *et al.* (2000)
Coxiella burnetti	Astobiza *et al.* (2012); Muskens *et al.* (2011); Rodolakis *et al.* (2007)
Foot-and-mouth disease virus	Reid *et al.* (2006); Thurmond and Perez (2006)
Mycobacterium avium subspecies *paratuberculosis*	Cousins *et al.* (1999); Jayaro *et al.* (2004); Slana *et al.* (2008); Tasara *et al.* (2005)
Mycoplasma bovis	Arcangioli *et al.* (2011); Justice-Allen *et al.* (2011); Maunsell *et al.* (2011)
Staphylococcus aureus	Haran *et al.* (2012); Zanardi *et al.* (2014)
Streptococcus agalactiae	Phuektes *et al.* (2003); Soltau *et al.* (2017)
Antibody detection	
Border disease virus	Berriatua *et al.* (2006); Corbiere *et al.* (2012); Garcia-Perez *et al.* (2010)
Bovine viral diarrhea virus	Foddai *et al.* (2015); Houe (1999); Hanon *et al.* (2017); Kramps *et al.* (1999); Lanyon *et al.* (2014); Renshaw *et al.* (2000)
C. burnetti	Muskens *et al.* (2011); van den Brom *et al.* (2012)
Foot-and-mouth disease virus	Armstrong *et al.* (1997*a*, 1997*b*); Armstrong, Mathew (2001)
M. avium subspecies *paratuberculosis*	Beaver *et al.* (2016); Nielsen *et al.* (2000); van Weering *et al.* (2007); Wilson *et al.* (2010)
M. bovis	Nielsen *et al.* (2015)
Schmallenberg virus	Balmer *et al.* (2014); Collins *et al.* (2017); Daly *et al.* (2015); Johnson *et al.* (2014)
Culture or isolation	
M. avium subspecies *paratuberculosis*	Slana *et al.* (2008)
M. bovis	Justice-Allen *et al.* (2011); Maunsell *et al.* (2011); Parker *et al.* (2017*a*,*b*)
S. aureus	Olde Riekerink *et al.* (2006, 2010)
S. agalactiae	Keefe (1997)

As opposed to individual animal samples, e.g. probang samples, swabs, or blood samples, aggregate samples can be collected without animal restraint. The use of aggregate samples in veterinary surveillance has grown in tandem with developments in diagnostic technology, e.g. nucleic acid-based assays and antibody assays specifically adapted to these specimens. The purpose of this article is to review the use of bulk tank milk and pen-based oral fluids in infectious disease surveillance of livestock populations.

Bulk tank milk samples

Bulk tanks are designed to cool, agitate, and store milk in bovine, ovine, and caprine grade A dairies. Among other requirements of the Pasteurized Milk Ordinance (U.S. Food and Drug Administration, 2015), bulk tanks must chill milk (4.4–7°C) within 2 h of collection and maintain this range thereafter. The size and number of bulk tanks vary among farms as a function of the number of animals in the herd or flock, but larger operations may have multiple tanks capable of storing thousands of gallons of milk. Milk haulers may collect once a day, more than once a day, or every other day, depending on the farm's storage capacity and milk production levels. Regardless of the collection schedule, bulk tanks must be emptied, cleaned, and sanitized at least every 72 h (Bickett-Weddle *et al.*, 2011; U.S. Food and Drug Administration, 2015).

In the context of disease surveillance, samples from bulk milk tanks represent the lactating cows in the herd (Sekiya *et al.*, 2013). Depending on the governmental standards or ordinances, tanks are agitated for ≥10 min after which samples are collected aseptically from the top of the tank using a sterile pipette, syringe, or sanitized dipper (Bickett-Weddle *et al.*, 2011; U.S. Food and Drug Administration, 2015). Although bulk tank milk samples do not represent dry cows or cows on milk withhold, they provide an economical, convenient, and timely approach for the detection of specific pathogens and/or estimation of herd prevalence (Olde Riekerink *et al.*, 2006; Sekiya *et al.*, 2013; Lanyon *et al.*, 2014; Collins *et al.*, 2017). Economically significant pathogens detectable in bulk tank milk samples and reported in the refereed literature are discussed below and listed in Table 1.

Schmallenberg virus

Schmallenberg virus (SBV) is an arthropod vector-borne orthobunyavirus first detected in dairy herds in Germany and the Netherlands in 2011 (Balmer *et al.*, 2014; Gubbins *et al.*, 2014; Johnson *et al.*, 2014; Daly *et al.*, 2015). SBV infection causes abortions, congenital malformations, diarrhea, and fever in bovine, ovine, and caprine species (Johnson *et al.*, 2014; Daly *et al.*, 2015; Collins *et al.*, 2017). The duration of SBV viremia is relatively short, i.e. an average of 3–4 days (Gubbins *et al.*, 2014), but SBV serum-neutralizing antibodies can be detected in cattle for as long as 24 months post-infection (Elbers *et al.*, 2014). The detection of SBV nucleic acid has not been reported

https://doi.org/10.1017/S1466252318000038 Published online by Cambridge University Press

in milk, but antibodies to SBV can be detected in an individual cow and bulk tank milk samples using commercial indirect enzyme-linked immunosorbent assay (ELISAs) (Balmer *et al.*, 2014; Johnson *et al.*, 2014; Daly *et al.*, 2015). Although test performance estimates are not available (diagnostic sensitivity, diagnostic specificity), results of bulk tank milk ELISA testing were predictive of within-herd seroprevalence and herd immunity (Collins *et al.*, 2017). Analyses based on bulk tank milk testing results have been used to assess the spatial distribution, rate of spread, direction of the spread, and effect of farm altitude on the prevalence of SBV (Balmer *et al.*, 2014; Johnson *et al.*, 2014).

Bovine viral diarrhea virus

First described in the 1940s, bovine viral diarrhea virus (BVDV) is a pestivirus transmitted through direct contact or fetal (*in utero*) infection (Goens, 2002). Clinical signs of BVDV include watery and/or bloody diarrhea, dehydration, pyrexia, tenesmus, tachypnea, and ulcers of the muzzle, lips, oral cavity, and/or nares (Goens, 2002).

BVDV antibodies can be detected in bulk tank milk samples using blocking, indirect, or competitive ELISAs (Houe, 1999; Kramps *et al.*, 1999; Renshaw *et al.*, 2000; Lanyon *et al.*, 2014; Foddai *et al.*, 2015; Hanon *et al.*, 2017). A Danish blocking ELISA demonstrated a diagnostic sensitivity of 100% and diagnostic specificity of 62% when testing bulk tank milk samples from herds with a BVDV prevalence of 26% (Foddai *et al.*, 2015). Diagnostic sensitivities and specificities of competitive ELISAs were reported as 97–100% and 99%, respectively; whereas the diagnostic sensitivities and specificities of indirect ELISAs were reported as 94–100% and 98% (Hanon *et al.*, 2017). As with SBV, bulk tank milk ELISA results were highly associated with herd seroprevalence (Lanyon *et al.*, 2014).

Persistently infected (PI) animals, the result of fetal infection during the first trimester of pregnancy (immunotolerance), serve as a continuous source of infection (Houe, 1999; Fray *et al.*, 2000; Renshaw *et al.*, 2000). PI cows produce little-to-no BVD antibody, but continuously shed real-time reverse transcription polymerase chain reaction (RT-rtPCR)-detectable levels of BVDV in milk (Radwan *et al.*, 1995; Kramps *et al.*, 1999; Houe, 1999; Renshaw *et al.*, 2000). Drew *et al.* (1999) reported 100% diagnostic sensitivity and specificity for PCR-based detection of BVDV RNA in bulk tank milk samples from herds with PI cows.

Strategically, antibody detection is used to identify the herds with circulating BVDV, and nucleic acid detection is used to identify the herds with PI cattle (Lanyon *et al.*, 2014). Monitoring changes in antibody prevalence has been used to determine whether a BVDV infection is ongoing or recent (Lanyon *et al.*, 2014). ELISA testing has also been used to monitor declining antibody levels after removal of PI cattle (Houe, 1999).

Border disease virus

First reported in England and Wales in 1958 and closely related to BVDV, border disease virus (BDV) is a pestivirus of ovine and caprine species (Nettleton *et al.*, 1998). BDV is transmitted through direct contact or transplacentally, with infection during early pregnancy resulting in PI offspring (Garcia-Perez *et al.*, 2010). Goats are susceptible to BDV, but infection is rare and typically results in abortion (Nettleton *et al.*, 1998). In sheep, clinical signs of BDV include abortion, stillbirths, and nonviable lambs.

As in the case of BVDV, PI animals shed BDV continuously and do not produce antibodies. Bulk tank milk samples can be tested for BDV by RT-rtPCR; however, estimates of diagnostic performance have not been reported (Berriatua *et al.*, 2006). Immunocompetent animals produce antibodies detectable in bulk tank milk (Garcia-Perez *et al.*, 2010). In one study, the diagnostic sensitivity and specificity of a blocking ELISA for BDV detection in bulk tank milk samples was reported as 100 and 85.2%, respectively (Corbiere *et al.*, 2012). A high seroprevalence of BDV in lactating animals suggests the presence of PI animals (Berriatua *et al.*, 2006). Thus, ELISA testing of bulk tank milk samples provides the means to estimate the prevalence of BDV in flocks and may indirectly reveal the presence of PI animals (Berriatua *et al.*, 2006; Garcia-Perez *et al.*, 2010).

Foot-and-mouth disease virus

FMDV is a highly impactful picornavirus of cloven-hoofed animals (Reid *et al.*, 2006; Thurmond and Perez, 2006; Knight-Jones and Rushton, 2013). FMDV can be transmitted by direct or indirect contact (Bravo de Rueda *et al.*, 2014). Clinical signs of FMDV infection include vesicular lesions, decrease in milk yield in lactating cattle, and pyrexia (Armstrong and Mathew, 2001).

FMDV was detected in milk samples from individual cows by RT-rtPCR for 23 days post-inoculation (Reid *et al.*, 2006). Estimates of the diagnostic sensitivity and specificity of RT-rtPCR for the detection of FMDV in bulk tank milk samples has not been reported, but Thurmond and Perez (2006) predicted that RT-rtPCR testing of bulk tank milk samples would detect FMDV 4–7 days earlier than detection based on the recognition/reporting of clinical signs.

FMDV antibodies may be detected in ovine and bovine milk using blocking ELISAs (Armstrong, 1997*a*, 1997*b*). Estimates for diagnostic sensitivity and specificity of these ELISAs are not available, but Armstrong and Mathew found a statistically significant correlation ($r = 0.53$) between serum and milk antibody titers (Armstrong and Mathew, 2001). On this basis, these researchers suggested that antibody testing of bulk tank milk samples would be an effective approach for monitoring herd immunity and/or evaluating population susceptibility to FMDV.

Mycobacterium avium *subspecies* paratuberculosis

Mycobacterium avium subspecies *paratuberculosis* (MAP) is the etiologic agent of Johne's disease in ruminants (Mortier *et al.*, 2014). Most commonly acquired via fecal–oral transmission, Johne's disease is characterized by enteritis, decreased milk yield, weight

https://doi.org/10.1017/S1466252318000038 Published online by Cambridge University Press

loss, diarrhea, and death (Wilson *et al.*, 2010; Mortier *et al.*, 2014). A causal role for MAP in Crohn's disease has been postulated, but was neither confirmed nor rejected by an assessment of the available data (Feller *et al.*, 2007).

MAP is detectable in milk via culture and PCR testing, but culture of bulk tank milk samples is not practical because the procedure is neither diagnostically sensitive nor timely, i.e. culture can take 18–52 weeks (Slana *et al.*, 2008). The most common target of PCR assays is multiple copy insertion sequence *IS900* in the MAP genome (Slana *et al.*, 2008). The analytical sensitivity of the *IS900* PCR is reported as 5–6 MAP cells ml^{-1} of bulk tank milk versus 83 MAP cells ml^{-1} for a PCR targeting *F57*. However, *IS900* PCRs may have issues with analytical specificity because of the homology of this region across mycobacteria species (Cousins *et al.*, 1999; Tasara *et al.*, 2005; Slana *et al.*, 2008). Jayaro *et al.* (2004) reported a diagnostic sensitivity of 21% and diagnostic specificity of 50% for bulk tank milk samples using an *IS900* PCR. No estimates of diagnostic sensitivity and specificity are available for *F57*-based PCRs.

ELISA-detectable MAP antibodies are present in bulk tank milk samples, but interpretation of testing results has not been clearly established (Nielsen *et al.*, 2000; van Weering *et al.*, 2007; Wilson *et al.*, 2010; Beaver *et al.*, 2016). Regardless, some researchers believe that ELISA testing of bulk tank milk samples can be used effectively by monitoring changes over time (van Weering *et al.*, 2007; Beaver *et al.*, 2016). Alternatively, Beaver *et al.* (2016), suggested the concurrent use of both assays for bulk tank milk monitoring programs for MAP (Beaver *et al.*, 2016). Thus, herds with positive PCR results and high ELISA titers reflected active infection; whereas, herds with positive PCR results but low ELISA titers reflected environmental contamination (Beaver *et al.*, 2016).

Coxiella burnetii *(Q fever)*

Coxiella burnetii is an obligate, intracellular rickettsial organism and the cause of Q fever in animals and humans (Kim *et al.*, 2005). Infection with *C. burnetii* results in reproductive disease, including metritis and infertility in cattle and abortion in goats and sheep (Kim *et al.*, 2005; Rodolakis *et al.*, 2007). Shedding patterns of *C. burnetii* in milk is species-dependent and varies among cattle, sheep, and goats (Rodolakis *et al.*, 2007). Cattle shed *C. burnetii* in milk for several months, goats shed for a shorter time, and sheep do not reliably shed in milk (Rodolakis *et al.*, 2007; Astobiza *et al.*, 2012). Antibody to and nucleic acids of *C. burnetii* are detectable in bulk tank milk samples with ELISA and PCR, respectively (Rodolakis *et al.*, 2007; van den Brom *et al.*, 2012). Muskens *et al.* (2011) reported diagnostic sensitivity and specificity of 82 and 70%, respectively, when testing bulk tank milk samples by a commercial real-time PCR. The diagnostic sensitivity and specificity of a commercial *C. burnetii* antibody ELISA for bulk tank milk was reported as 88.2 and 94.6%, respectively, using manufacturer-recommended cutoffs (van den Brom *et al.*, 2012). When used in combination, ELISA testing of bulk tank milk samples can be used to determine herd exposure and estimate prevalence of *C. burnetii*, while PCR testing can be used to determine shedding and prevalence (Muskens *et al.*, 2011; Astobiza *et al.*, 2012).

Detection of bacterial pathogens associated with mastitis

Streptococcus agalactiae is a highly contagious, obligate pathogen of the bovine mammary gland and a cause of subclinical and clinical mastitis (Keefe, 1997; Phuektes *et al.*, 2003; Olde Riekerink *et al.*, 2006; Mweu *et al.*, 2012). *Streptococcus agalactiae* may be detected in bulk tank milk samples by culture or PCR (Keefe, 1997; Phuektes *et al.*, 2003). As reviewed by Phuektes *et al.* (2003), estimates of the diagnostic sensitivity of culture range from 20 to 84%. Estimates of the diagnostic sensitivity and specificity are not available, but as would be expected, testing multiple bulk tank milk samples was shown to increase the likelihood of detecting *S. agalactiae* by PCR (Phuektes *et al.*, 2003; Soltau *et al.*, 2017). ELISA-detectable *S. agalactiae* antibodies have been reported in individual milk samples, but this approach has not been evaluated for bulk tank milk testing (Logan *et al.*, 1982).

Staphylococcus aureus is an opportunistic pathogen and a cause of subclinical and clinical mastitis in cattle, sheep, and goats (Olde Riekerink *et al.*, 2006; Haran *et al.*, 2012; Zanardi *et al.*, 2014; Merz *et al.*, 2016). As reviewed by Olde Riekerink *et al.* (2010), culture of bulk tank milk for *S. aureus* had an estimated diagnostic sensitivity of 21–42% and a diagnostic specificity of 100%. Repeated sampling is recognized to improve the probability of detection by culture (Olde Riekerink *et al.*, 2006, 2010). PCR testing of bulk tank milk samples can be used to detect *S. aureus*, estimate herd prevalence of the infection, and assess for the presence of methicillin-resistant strains (Haran *et al.*, 2012). The diagnostic sensitivity and specificity of PCR testing for *S. aureus* in bulk tank milk samples is reported at 99 and 67%, respectively (Zanardi *et al.*, 2014). Using individual milk, ELISA testing for antibodies against *S. aureus* may be used to as a screening tool to detect infected animals (Fox and Adams, 2000).

Mycoplasma bovis is a highly pathogenic mycoplasma causing both mastitis and respiratory disease in adult cattle (Parker *et al.*, 2017*a*). *Mycoplasma bovis* is detectable in bulk tank milk samples by culture, but the assay can take 7–10 days and overgrowth of bacteria is problematic (Parker *et al.*, 2017*a*, 2017*b*). The diagnostic sensitivity of *M. bovis* culture is reported as 50%, with diagnostic specificity estimates as high as 100% (Justice-Allen *et al.*, 2011; Maunsell *et al.*, 2011). The diagnostic sensitivity and specificity of *M. bovis* PCR for individual milk samples is reportedly 100 and 99.3%, respectively, but estimates of PCR performance for bulk tank milk samples have not been reported (Cai *et al.*, 2005). PCR testing allows for more rapid detection of *M. bovis* versus culture and herd prevalence estimates can be extrapolated from the results (Arcangioli *et al.*, 2011). A commercial antibody ELISA is available for bulk tank milk testing, and estimates for diagnostic sensitivity and specificity are 60.4 and 97.3%, respectively (Nielsen *et al.*, 2015). The combination of PCR and ELISA testing can reveal

https://doi.org/10.1017/S1466252318000038 Published online by Cambridge University Press

M. bovis infection in a herd and is an effective approach for surveillance (Nielsen *et al.*, 2015).

Oral fluid samples

Oral fluids are collected from swine or cattle by providing access to a rope suspended in the pen, then recovering the sample for diagnostic testing (Smith *et al.*, 2004; Prickett *et al.*, 2008*a*, 2008*b*; Stanford *et al.*, 2009; Prickett *et al.*, 2010). Oral fluid samples are an aggregate sample composed of saliva and transudate originating from capillaries within the buccal and gingival mucosa (Prickett *et al.*, 2008*a*). Oral fluids contain both local and serum-derived antibodies and pathogens (Prickett *et al.*, 2008*a*, 2008*b*; Prickett and Zimmerman, 2010). In addition, viruses, bacteria, and other test analytes in feed, water, or the environment may be present in oral fluids as a result of normal exploratory behavior (Kittawornrat and Zimmerman, 2011; Johnson *et al.*, 2012). This explains the detection of porcine epidemic diarrhea virus (PEDV) in swine oral fluid samples and *Escherichia coli* and salmonella in cattle (Smith *et al.*, 2005*a*, 2005*b*; Renter *et al.*, 2008; Bjustrom-Kraft *et al.*, 2016). In cattle, oral fluids have been used in the observational studies in feedlot cattle (Renter *et al.*, 2008; Smith *et al.*, 2005*a*, 2005*b*), but have not been routinely utilized in surveillance. In contrast, oral fluids have been used extensively for disease surveillance in swine populations. Therefore, the remainder of this section will focus exclusively on this subject.

Oral fluids can be collected from groups or individual pigs (White *et al.*, 2014; Pepin *et al.*, 2015*a*, 2015*b*). In group-housed animals, oral fluids offer a higher probability of detection with fewer samples when compared with individual serum samples (Olsen *et al.*, 2013). Sampling guidelines for oral fluid collection at the barn or site level have been published (Rotolo *et al.*, 2017).

Diagnostic assays optimized for swine oral fluid specimens have been available in North American veterinary diagnostic laboratories since 2010 (Olsen *et al.*, 2013; Bjustrom-Kraft *et al.*, 2018). In three North American swine-interest veterinary diagnostic laboratories, the number of oral fluid tests performed increased from 20,963 in 2010 to 369,439 in 2016 (Bjustrom-Kraft *et al.*, 2018). Pathogens detectable in oral fluid samples and reported in the refereed literature are listed in Table 2. Selected pathogens are reviewed below.

Foot-and-mouth-disease virus

Rapid screening of swine herds is critical in the control of FMDV because pigs aerosolize a large amount of virus compared with cattle and promulgate virus transmission (Stenfeldt *et al.*, 2016). Under experimental conditions, FMDV was isolated from swine oral fluids on day post-inoculation (DPI) 1–5 (Senthilkumaran *et al.*, 2017). By RT-rtPCR, FMDV was detected from one DPI, i.e. prior to the appearance of clinical signs, and up to 21 DPI (Mouchantat *et al.*, 2014; Senthilkumaran *et al.*, 2017). RNA was detected in oral fluids one day earlier than oral or nasal swab samples and continued ~7 days longer (Senthilkumaran *et al.*, 2017). A field-deployable reverse transcription-insulated isothermal PCR has also been used to detect FMDV RNA in oral fluids (Ambagala *et al.*, 2016). FMDV antigens were detected in oral fluids 1–6 DPI using lateral flow immunochromatographic strip tests and 2–3 DPI using a double-antibody sandwich ELISA (Senthilkumaran *et al.*, 2017). FMDV IgA was detected in oral fluids using a solid-phase competitive ELISA beginning at 14 DPI (Senthilkumaran *et al.*, 2017). Pacheco *et al.* (2010) were not successful in detecting FMDV IgM or IgG in oral fluid samples. Estimates of diagnostic sensitivity and specificity have not been reported for the assays reported in this paragraph. Although FMDV oral fluid assay development is in its early stages, preliminary results support the use of nucleic acid and antibody detection as a method to rapidly screen herds (Ambagala *et al.*, 2016; Senthilkumaran *et al.*, 2017).

Classical swine fever virus

CSFV is a pestivirus with significant economic consequences resulting from clinical disease, lost export markets, and costs related to control and eradication efforts (Fernández-Carrión *et al.*, 2016). CSFV can be transmitted by direct or indirect contact and, depending on the virulence of the strain, causes pyrexia, anorexia, lethargy, conjunctivitis, enlarged and discolored lymph nodes, constipation, and diarrhea in affected pigs (Moennig *et al.*, 2003; Petrini *et al.*, 2017). Under experimental settings, CSFV was detected in oral fluids by RT-rtPCR from seven up to 30 DPI, with a higher detection rate in oral fluid than blood samples (40 vs 28%) (Dietze *et al.*, 2017; Petrini *et al.*, 2017). Estimates of diagnostic sensitivity and specificity have not been reported for these assays and, overall, research on CSFV oral fluid diagnostics is in its initial phases.

African swine fever virus

Infection with African swine fever virus (ASFV), the only member of family *Asfarviridae*, is a cause of fever, hemorrhage, and mortality in domestic and feral pigs (Sanchez-Vizcaino and Neira, 2012; Guinat *et al.*, 2014; Gimenez-Lirola *et al.*, 2016). Transmitted through direct and indirect contact, ASFV is of particular concern because, since its introduction into the Democratic Republic of Georgia in 2007, it has steadily advanced westwardly into Europe via feral swine and threatens to spread eastwardly into China (Guinat *et al.*, 2014; Vergne *et al.*, 2017).

Under experimental conditions, ASFV was detected in oral fluid 3–5 DPI by PCR (Guinat *et al.*, 2014; Grau *et al.*, 2015). ASFV antibodies were detected at 11 DPI in individual oral fluid samples by indirect ELISA under experimental conditions (Mur *et al.*, 2013). The pattern of antibody response in oral fluids was similar to the pattern seen in serum (Mur *et al.*, 2013). ASFV antibodies were also detected using a p30-based indirect ELISA in oral fluids (Gimenez-Lirola *et al.*, 2016). Diagnostic sensitivities and specificities for these assays have not been reported. As in the cases of FMDV and CSFV, further studies are needed

https://doi.org/10.1017/S1466252318000038 Published online by Cambridge University Press

Table 2. Pathogens detected in oral fluid

Method	Reference
Nucleic acid detection	
African swine fever virus	Grau *et al.* (2015); Guinat *et al.* (2014)
Classical swine fever virus	Dietze *et al.* (2017); Petrini *et al.* (2017)
Foot-and-mouth disease	Ambagala *et al.* (2016); Mouchantat *et al.* (2014); Senthilkumaran *et al.* (2017)
Influenza A virus	Allerson *et al.* (2014); Decorte *et al.* (2015); Goodell *et al.* (2013); Romagosa *et al.* (2012)
Porcine deltacoronavirus	Homwong *et al.* (2016); Sinha *et al.* (2015)
Porcine epidemic diarrhea virus	Bjustrom-Kraft *et al.* (2016)
Porcine reproductive and respiratory syndrome virus	Biernacka *et al.* (2016); Kittawornrat *et al.* (2010, 2014); Pepin et al. (2015*a*, 2015*b*); Prickett et al. (2008*a*, 2008*b*); Olsen *et al.* (2013); Ramirez *et al.* (2012); Rotolo *et al.* (2017)
Antigen detection	
Foot-and-mouth disease	Senthilkumaran *et al.* (2017)
Antibody detection	
African swine fever virus	Gimenez-Lirola *et al.* (2016); Mur *et al.* (2013)
Influenza A virus	Panyasing *et al.* (2013, 2014*b*); Strutzberg-Minder *et al.* (2015)
Porcine epidemic diarrhea virus	Bjustrom-Kraft *et al.* (2016)
Porcine reproductive and respiratory syndrome virus	Kittawornrat *et al.* (2013); Langenhorst *et al.* (2012)
Culture or isolation	
Influenza A virus	Goodell *et al.* (2013)

to optimize ASFV oral fluid assays and assess their use in the field (Grau *et al.*, 2015).

Porcine reproductive and respiratory syndrome virus

PRRSV is an arterivirus transmitted through direct and indirect contact (Zimmerman *et al.*, 2012). Clinical signs of PRRSV vary based on the age of the pig and the virulence of the isolate. In sows, clinical signs include abortion, stillbirths, anorexia, and mortality (Zimmerman *et al.*, 2012). PRRSV is often an etiological component of the porcine respiratory disease complex in growing pigs (Zimmerman *et al.*, 2012).

The detection of PRRSV nucleic acid in oral fluids has been extensively documented under field and experimental conditions (Prickett *et al.*, 2008*a*, 2008*b*; Kittawornrat *et al.*, 2010, 2014; Ramirez *et al.*, 2012; Pepin *et al.*, 2015*a*, 2015*b*; Rotolo *et al.*, 2017). Kittawornrat *et al.* (2010) reported detection in ∼10% of experimentally inoculated boars at 24 h post-inoculation by RT-rtPCR. Olsen *et al.* (2013) evaluated test performance as a function of within-pen prevalence. In pens holding 25 pigs, the probability of detecting PRRSV RNA or PRRSV antibody in pens containing ≥1 positive (4% prevalence) was 62 and 61%, respectively. PRRSV may also be sequenced from oral fluids (Biernacka *et al.*, 2016).

IgG, IgA, and IgM antibody isotypes were detected in oral fluids collected from individual boars using a commercial PRRS serum antibody indirect ELISA modified for oral fluids (Kittawornrat *et al.*, 2013). The pattern of PRRSV antibody ontogeny was similar in serum and oral fluid, with IgM detected in oral fluids at three DPI, IgA at seven DPI, and IgG at eight DPI (Kittawornrat *et al.*, 2013). Commercial PRRSV oral fluid ELISAs have since become available. Antibodies were also detected in oral fluid using a fluorescent microsphere immunoassay with a reported diagnostic sensitivity of 92% and diagnostic specificity of 91% (Langenhorst *et al.*, 2012).

Testing of oral fluids can be used to assess the effectiveness of PRRSV control and elimination programs (Biernacka *et al.*, 2016; Rotolo *et al.*, 2017). A distinct advantage of PRRSV oral fluid-based surveillance is that pen-based oral fluid sampling provides a higher probability of detection than individual animal sampling using either RT-rtPCR or ELISA (Olsen *et al.*, 2013).

Influenza A virus

Influenza A virus (IAV) is an orthomyxovirus of human beings, horses, sea mammals, birds, and pigs, transmitted via direct and indirect contact (Hughes *et al.*, 2015; Neira *et al.*, 2016). IAV in commercial swine herds results in chronic, endemic infection with respiratory or reproductive clinical signs, as well as clinically inapparent infections (Goodell *et al.*, 2013; Panyasing *et al.*, 2013). IAV is an important pathogen to surveil in pigs because of its zoonotic potential (Vincent *et al.*, 2014; Hughes *et al.*, 2015).

Under experimental conditions, IAV RNA was detected in swine oral fluids by one DPI and up to 69 DPI (Allerson *et al.*, 2014; Decorte *et al.*, 2015). Decorte *et al.* (2015) reported the duration of detection in oral fluids as 14 days longer than detection in nasal swabs by RT-rtPCR (Decorte *et al.*, 2015). Compared with individual nasal swabs, the diagnostic sensitivity and specificity of pen-based oral fluid RT-rtPCR testing was estimated at 80 and 100%, respectively (Romagosa *et al.*, 2012). Although further optimization is necessary, IAV has also been isolated from oral fluids (Goodell *et al.*, 2013). Sequencing of IAV from oral fluids has been reported (Panyasing *et al.*, 2014*a*). RT-rtPCR testing of oral fluids can

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be used to track viral circulation and to monitor the effect of vaccination and control programs in commercial swine herds (Goodell *et al.*, 2013).

Panyasing *et al.* (2013) reported the ontogeny of IAV IgM, IgA, and IgG in pigs housed under experimental conditions, using isotype-specific indirect ELISAs. Serum and oral fluid IgG responses were highly correlated ($r = 0.80$) (Panyasing *et al.*, 2013). Detection of IAV antibody has also been reported using blocking or competitive ELISA formats (Panyasing *et al.*, 2014*b*; Strutzberg-Minder *et al.*, 2015). Diagnostic sensitivity and specificity estimates have not been established for these assays. Antibody detection in oral fluids allows for the detection of IAV infection in the absence of clinical signs (Panyasing *et al.*, 2013).

Coronaviruses

PEDV is an enteric coronavirus transmitted via the fecal–oral route (Crawford *et al.*, 2015; Bjustrom-Kraft *et al.*, 2016). Clinical signs of PEDV infection in swine include watery diarrhea, vomiting, and mortality in neonates (Bjustrom-Kraft *et al.*, 2016). In the field, Bjustrom-Kraft *et al.* (2016) reported the detection of PEDV nucleic acid in oral fluids from 6 days post-exposure (DPE) to 69 DPE. PEDV was detected 15 days longer in oral fluid samples compared with pen fecal samples, and, compared with individual rectal swabs, oral fluids demonstrated a higher concentration of detectable virus and higher rate of detection. In the same study, Bjustrom-Kraft *et al.* (2016) reported the detection of PEDV antibody (IgG and IgA) by 13 DPE in oral fluids. The diagnostic sensitivity and specificity of a PEDV IgG oral fluid ELISA was reported as 69 and 97%, respectively. In contrast, the diagnostic sensitivity and specificity of a PEDV IgA oral fluid ELISA were reported as 100 and 100%, respectively (Bjustrom-Kraft *et al.*, 2016). Although estimates of diagnostic sensitivity and specificity have not been reported, the oral fluid RT-rtPCR is an effective tool to monitor for PEDV presence in herds, and IgA antibody testing offers an effective method to evaluate herd-level immunity (Bjustrom-Kraft *et al.*, 2016).

Like PEDV, porcine deltacoronavirus (PDCoV) is an enteric coronavirus that causes diarrhea and vomiting in pigs (Homwong *et al.*, 2016). PDCoV can be detected in oral fluids by RT-rtPCR, although estimates of diagnostic sensitivity and specificity are not available (Sinha *et al.*, 2015; Homwong *et al.*, 2016; Zhang, 2016). Homwong *et al.* (2016) reported that the detection of PDCoV nucleic acid in oral fluids was 1.89 times more likely than detection in feces. PDCoV antibody ontogeny in serum and oral fluids has not yet been reported.

Discussion

Globally, the production of livestock – poultry, cattle, and swine – is in the process of shifting from small populations on many farms to large populations on fewer farms (Hoban *et al.*, 1997; Marquer, 2010; Barkema *et al.*, 2015; Gale, 2017). Readily accessible USDA data from the dairy and swine industries highlight this trend. In 1982, ~275,000 US dairy farms housed ~11,000,000 dairy cows. By 2012, the number of dairy farms dropped to ~64,000, while animal numbers remained relatively stable at ~9,250,000 (USDA, 2014). Pork production has followed the same trend. In 1982, ~330,000 US farms housed ~55,000,000 pigs in 1982. By 2012, the number of farms with pigs declined to ~63,000, while the number of pigs increased to ~66,000,000 (USDA, 2014). Increases in herd size are important to disease control because herd immunity becomes more difficult to achieve as population increases, which in turn leads to pathogen endemicity (LeBlanc *et al.*, 2006; Pitzer *et al.*, 2016).

Over the same time period, a shift occurred in the movement of livestock across political boundaries. In 1960, 13,500,000 live cattle crossed US state lines for feeding or breeding purposes (Hennessy *et al.*, 2005). By 2015, this number had risen to 20,500,000 (USDA, 2017). Similarly, ~2,500,000 pigs were moved across US stateliness in 1960, in contrast to ~52,500,000 moved in 2016 (Shields and Mathews, 2003; USDA, 2017). Similar patterns have emerged in Europe. For example, Denmark, France, Germany, Italy, the Netherlands, Poland, and Spain cumulatively imported ~910,000 live pigs and exported ~937,000 live pigs in 1961 (FAO, 2017). In contrast, these countries imported ~22,000,000 live pigs and exported ~27,000,000 in 2013 (FAO, 2017). Trends in livestock movement are important because of the well-established role of animal transport in the spread of disease, e.g. the 2001 FMDV outbreak in the UK and, more recently, spread of PEDV throughout the Western Hemisphere (Davies, 2015; Guinat *et al.*, 2016).

The unintended consequences of changes in the structure and management of livestock populations have manifested themselves in the appearance of multifactorial diseases resistant to traditional methods of prevention and control, e.g. bovine and porcine respiratory disease complexes (Schwabe, 1982; Gardner *et al.*, 2002; Hagglund *et al.*, 2006; LeBlanc *et al.*, 2006; Bochev, 2007; Edwards, 2010; Pitzer *et al.*, 2016). The need to understand complex animal health conditions mandates a shift toward the collection of longitudinal animal health data. New intervention strategies or unanticipated events, e.g. the introduction of an exotic pathogen, can then be evaluated in the context of their impact on baseline values.

Cumulatively, peer-reviewed research supports the conclusion that aggregate samples offer the opportunity to expand the scope of applied surveillance. Testing of bulk tank milk samples provides bovine and small ruminant practitioners and producers the means to monitor disease and estimate herd prevalence and provides animal health researchers the means to evaluate the spatial distribution and rate of disease transmission (Berriatua *et al.*, 2006; Garcia-Perez *et al.*, 2010; Balmer *et al.*, 2014; Johnson *et al.*, 2014; Collins *et al.*, 2017). Swine oral fluids offer a more analytically sensitive detection system than individual pig samples, and at a lower cost (Goodell *et al.*, 2013; Olsen *et al.*, 2013). Continued progress toward the goal of effective surveillance using aggregate sampling requires research in two areas: (1) continued development and adaption of diagnostic technology for the most globally impactful diseases of animals and human beings (zoonoses); (2) continued development of

https://doi.org/10.1017/S1466252318000038 Published online by Cambridge University Press

statistically valid sampling guidelines including probability of detection estimates by sample size, sampling allocation, and frequency of sampling for farm and regional surveillance.

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