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REVIEW ARTICLE

Salmonella Abortusovis: An Epidemiologically Relevant Pathogen

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Abstract
The ovine pathogen *Salmonella enterica* serovar Abortusovis (SAO), a pathogen strictly adapted to ovine hosts, is endemic in several European and Asian countries, where it causes significant economic losses due to the high rates of abortion in infected flocks. In some countries (i.e. Switzerland and Croatia), re-emergence of infection by SAO occurred after decades during which the disease has not been reported. The introduction of (SAO) epidemic strains in new areas is difficult to control due to the asymptomatic behaviors in infected adult lambs, rams, and nonpregnant ewes. Culture-based diagnosis may provide false-negative results. Moreover, the retrospective identification of *Salmonella* infection in ewes is challenging as excretion of the causative agent is transient and the serum antibodies fall to low titres soon after the abortion. Therefore, regular monitoring of pathogen exposure, mainly through seroconversion assessment, is advisable to prevent disease introduction and spread in SAO-free areas, especially in case of animal export, and to reduce abortion risk.

Introduction

Salmonella enterica subspecies *enterica* serovar Abortusovis (SAO) is a member of the *Enterobacteriaceae*. It is a pathogenic serovar host-adapted to sheep, able to cause infections that are mainly characterized by abortion as a main symptom. For this reason, SAO represents a major threat to the flocks and may result in important economic losses in regions that depend on shepherding.

Salmonellosis caused by this pathogen is reportable to the World Organization for Animal Health (OIE): outbreaks have been reported in southern Europe and Western Asia, but are uncommonly described outside those regions [1].

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However, surveillance can be sometimes challenging due to the reported difficulties in laboratory identification [2] and the asymptomatic behaviors of some infected animals [3].

Therefore, SAO infections can result underdiagnosed in some areas, and this could explain sudden re-emergence of the disease in some countries after decades during which it has not been reported [4]. Other control measures include vaccines and antibiotic therapy. Inactivated and live-attenuated vaccines against SAO have been developed and evaluated for their efficacy to prevent paratyphoid abortion, although a variety of results has been described [5]. For this reason, keeping alert on surveillance is essential to prevent infection spread, especially in case of live animal movement and exportation.

This review intends to raise attention towards this bacterial species and the related disease.

General characteristics and pathogenic features of SAO, including updated epidemiological data about the diffusion of the related infection, are illustrated. In our knowledge, this is the first comprehensive review addressing general characteristics and taxonomy, clinical signs and transmission, epidemiology, diagnosis and control measures for SAO and the relative infection. Thus, it can provide complete information to the reader who intends acquiring knowledge about this pathogen and the related epidemiological scenario.

Reliable diagnosis is a key element for the prevention of infection spread, especially if directed to the identification of infected individuals before their introduction in herds,

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that are the main source of outbreaks. However, the existing different diagnostic approaches showed advantages and limitations, according to the situation in which they should be used, especially if considering the absence of clinical signs in infected adult animals. Pros and cons of main diagnostic methods in use are summarized here, highlighting the importance of targeted and scanning surveillance as the most important way to control infection spread, especially if integrated with molecular typing of isolates.

This review would like to contribute to this topic, discussing in depth all disputable issues of all diagnostic methods and illustrating their potential capacities and drawbacks for the prevention of infection re-emergence and/or containment. Finally, the question under discussion is if a regular monitoring, especially through seroconversion assessment, is useful to prevent disease introduction and to reduce abortion risk in SAO-free areas.

Discussion

General Characteristics and Taxonomy

The bacterial genus *Salmonella* comprises aerobic, Gram negative rods. This genus includes two species: *S. enterica* and *S. bongori* [6]. According to biochemical characters and phage susceptibility, each species has been divided in subspecies, and on the basis of lipopolysaccharide (LPS) and flagellar antigens, furtherly classified in serovars (White-Kauffmann–Le Minor scheme); currently, more than 2600 serovars are recognised [7]. *Salmonella* serovars differ in the range of hosts they can infect and in the nature of disease that may result; this difference is referred to as serovar-host specificity.

The most common serovars of veterinary and human clinical interest belong to subspecies *enterica*. SAO is a member of this subspecies.

Clinical Features and Transmission

SAO is a host-restricted serovar, thus highly specific for sheep, and no human infections have been reported [2]. In contrast to other *Salmonella* infections, infection with SAO rarely results in gastrointestinal disease, although fecal excretion has beed described [8] and SAO DNA was detected in feces [2]. Indeed, like some other host-specific serovars, SAO often displays tropism for lymphatic organs and causes septicaemic disease and abortion [9].

The major clinical signs in infected naïve flocks are abortions occurring in the last trimester in 30–50% of pregnant ewes, in the absence of other clinical symptoms. In endemically infected flocks, the incidence decreases to an average of 10% as a result of background protective immunity, and abortions are usually limited to recently purchased sheep or ewes lambing for the first time [10, 11].

SAO may also cause stillbirths and deaths of lambs under one month of age. Neverthless, many animals could be infected without showing clinical signs [3]. These animals have an important epidemiologic role in disease spread.

Concerning transmission, infection is usually introduced in one flock by carrier sheep. The main source of infection during the lambing season are the aborted fetus, placenta and vaginal discharges [2]. The transmission occurs by the faecal-oral route, but not by feed, water or faeces; additionally, respiratory secretions may spread the infection [3].

Geographical Distribution and Epidemiology

SAO is one of the leading causes of abortion in sheep. Epidemiological data about occurrence of SAO in year interval 2005–2021 can be retrieved on the World Animal Health Information Database (WAHIS) interface of OIE (https://old.oie.int/wahis_2/public/wahid.php/Diseaseinformation/statusdetail), reporting the list of world countries by disease situation (never occurred; disease absent during the report period; disease suspected or confirmed; infection present without clinical cases; limited to one/more zones; demonstrated clinical cases). Data are also available at: https://wahis.oie.int/#/dashboards/country-or-disease-dashboard. In most countries where sheep husbandry is widely performed, such as the UK, Australia, New Zealand and the USA, sheep salmonellosis is apparently rare; however, prevalence of SAO infection is more relevant in southern Europe (Italy, Spain, France, Germany, Cyprus, Greece, Switzerland, Bulgaria, Romania), Russia, the Middle East/western Asia and northern Africa [3, 12–16].

Between 2005 and 2019, infections or outbreaks were reported in some European countries, Russia, parts of Asia, some islands (e.g., New Caledonia, Cook Islands), and a few countries in the Middle East, Africa and South America. Other countries in the same regions never reported cases of SAO infection, or referred that the last outbreak occurred in the 1990s or earlier. In North America, Canada last registered SAO in 1994; the status of the U.S. is described in OIE reports as “disease suspected but not confirmed”, and Mexico has never diagnosed this disease [1].

In areas of endemicity, abortion can affect 30 to 50% of the ewes of an infected flock, but rates up to 90% have been reported [1, 17] causing serious damage in regions with a sheep-based economy.

In Switzerland a re-emergence of infection by SAO occurred after 27 years during which the disease has not been reported [18]. This country experienced abortion storms in years 2003–2007 and laboratory examination revealed an infection by SAO. The Swiss outbreak clone was not introduced from regions close to Switzerland but from

places in Europe from where no isolates have been identified and compared [2]. Infections with SAO are quite common in Switzerland, although cases are rarely reported, despite the fact that infection is notifiable [4]. This is likely due to the fact that there is insufficient awareness of and/or inadequate diagnostic techniques to detect this infection [10].

Similarly to the Swiss case, in which an outbreak occurred after a long period of undiagnosed or sporadic (but not reported) disease, Croatia also experienced an outbreak (winter 2003–2004) with 22–38% abortion rates after a first reporting in 1948 [19] and only sporadic subsequent identifications during the time of lambing [20].

Molecular techniques, such as pulsed field gel electrophoresis (PFGE), IS200 fingerprinting, ribotyping and plasmid profiling have been applied to the epidemiology of SAO, with the aim to trace SAO strain spread and to identify circulating genotypes [2, 15, 17, 21–23]. Results of these studies highlighted that the same endemic area, and sometimes the same affected flock, can be colonised by a wide number of clones [3]. Analysis targeted to the insertion element IS1414 allowed to discriminate two different epidemiologic clusters on the basis of presence and copy number of that sequence: one of them is diffused in Europe, the other predominates in Asia [24].

Diagnosis of SAO Infection

Diagnosis of SAO infection should be based on culture and identification of the bacteria, together with clinical and pathological evidence. Laboratory analysis can be accomplished by direct or indirect methods (Fig. 1). Direct diagnosis is based on the demonstration of pathogen presence in clinical samples. In the attempt to identify the microbial agent responsible for abortion, appropriate samples should be obtained and submitted to the laboratory, since sample selection is a key aspect for diagnosis reliability. A complete approach has been suggested by Borel et al. [10]. Clinical samples should be preferably collected during the acute phase of the disease. Indeed, the retrospective identification of *Salmonella* infection in ewes is challenging as excretion of the causative agent is transient and the serum antibodies fall to low titres soon after the abortion [2, 8, 25].

The bacteria can be isolated from vaginal discharge (swab), where they are shed after abortion: high bacterial loads are detected within 1 week. SAO can be also detected from fetal membranes (placenta), aborted fetus, liver, spleen, stomach (abomasus) contents and ewes' feces.

A combination of agent identification methods applied on the same clinical sample is recommended by the OIE Manual of diagnostic tests and vaccines for terrestrial animals [26], taking into account that the bacteria are still culturable after 1 month and PCR may still test positive after 1 year [2].

Culture

The ISO 6579-1:2017 [27] is the official method for the detection of *Salmonella* spp. suitable also for samples of the primary production stage. The method, which is not specific for SAO, includes a pre-enrichment in liquid media to recover sub-lethally damaged cells, a selective enrichment and a final plating on selective agar plates. However, some adaptations should be applied in case of SAO. First of all, this is a slow-growing pathogen requiring 36–48 h for colony formation in solid media, and occasionally it does not reach a significant size until 72 h [1]. Moreover, it has been showed that common *Salmonella*-selective media decrease sensitivity of SAO detection, and non selective blood agar should be used [26]. Pre-enrichment also decreases sensitivity, probably due to growth inhibition by *Escherichia coli* wild-type strains found in the intestinal content of sheep. *E. coli* from the digestive tract of sheep could inhibit the growth of SAO in vitro suggesting that the lower sensitivity of diagnosis by bacterial culture may in part be due to growth inhibition of

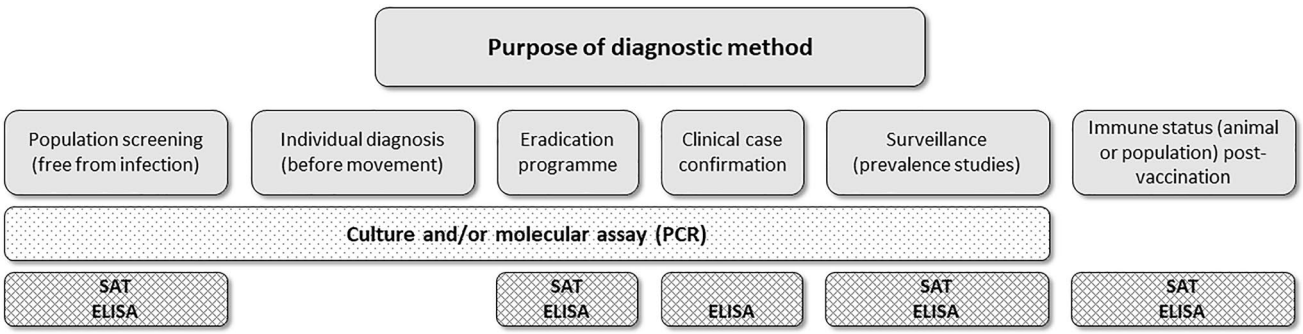

Fig. 1 Test methods available for the diagnosis of salmonellosis and their purpose. (From OIE Manual, modified). Infection could be recognised by agent direct identification through culture isolation or molecular assay (grey dots) or by detection of immune response through Serum Agglutination Test (SAT) or Enzyme-Linked Immunosorbent Assay (ELISA) (grey grid)

SAO by resident bacteria. For this reason, negative culture results should be considered with caution [2].

The limit of detection of culture methods has been estimated at 6.5×10^3–6.5×10^4 CFU/g [28].

Finally, characterization by standard biochemical tests (API 20E) could give inconsistent results because this procedure does not distinguish between SAO and *S. typhi* [21].

Molecular Diagnosis

Genomic information about SAO is increasingly available [29] and PCR-based methods have been developed, most of them targeting the serovar-specific insertion sequence IS200. Molecular methods have been used for colony identification or amplification of DNA directly extracted from samples [2, 12, 20, 29–32].

PCR allowed to identify SAO DNA in fecal and vaginal samples up to three months after infection [2], and twelve months after abortion [20], even in samples that were negative by culture, thus it gives added value in pathogen diagnosis, mainly in asymptomatic carriers.

When using DNA-based methods, inhibition of the amplification by molecules of sample matrix, especially in the case of faeces, is problematic [33] and requires suitable DNA extraction techniques and controls [34].

Other techniques, such as PFGE or nucleic acid hybridisation, have been applied for epidemiologic tracing and strain fingerprinting [15, 22].

A wide genetic heterogeneity in circulating genotypes has been reported in Europe, also within the same outbreak [2, 15, 23]. Moreover, SAO strains carry a serovar-specific insertion sequence IS1414 [24] indicating frequent recombination events. Finally, microarray analysis suggested extensive genome reduction in SAO genome, compatible with its host-restricted profile [35, 36].

Indirects methods consist mainly of serological assays, like the Serum Agglutination Test (SAT) and the Enzyme-Linked Immunosorbent Assay (ELISA). Some serological tests have been developed and applied for the detection of SAO infection and epidemiological surveillance of the disease [4, 11, 20, 37].

Serological assays are particularly useful to identify subclinically infected animals, such as rams, which develop a serological response but remain clinically normal [38].

However, serological diagnosis may be affected by some factors. The detection of IgG occurs typically within 1–3 weeks after infection, thus animals in the initial phases of the disease may be infectious despite of a serological negative result; similarly, if the serological test is performed after abortion, false-negative results may occur, due to the drop of antibody levels, which may become undetectable after 2–3 months [16, 39]; finally, it has been reported that some infected animals never seroconvert [26]. On the contrary, animals testing positive at serological assays sometimes do not excrete salmonellae but have high circulating immunoglobulin concentrations. Seropositivity, besides exposure to the pathogen, may also results from vaccination. Thus, positive results not always are indicative of active infections [26, 40]. For these reasons, serological diagnosis, conducted on a statistically representative sample of the population, may be more appropriately used to identify infected flocks, rather than individual animals [26]. Moreover, serological investigation appears to be useful in diagnosing non-endemic infections and/or infections against which animals are not vaccinated, can be applied to give information in areas in which disease has been eradicated [10], and it is better used for flock periodic surveillance instead of point prevalence.

However, the dynamics of immune responses aganist SAO should be better investigated when serological assays are to be used [37].

It has been noticed that antibiotic therapy can have unclear effects on the serological response or may reduce antibody titres. Serology, however, may be a more useful diagnostic technique for salmonellosis than culture if antimicrobial therapy has been used [26].

Finally, it is important to underline that inconclusive results could be found sometimes in serological diagnosis: since maternal infection can precede abortion by weeks, at the time of abortion the antibody titer could be decreased [37].

SAT

SAT is based on the detection of antibodies (mainly IgM) against a LPS antigen prepared by the laboratory. Sheep are found to be positive from 3 weeks to 3 months from the infection [4]. It is a low-cost method, with low sensitivity, especially in old animals [26]. SAT has lower sensitivity in comparison with ELISA tests [28, 41, 42].

However, a seroagglutination test may offer a strong presumption at the flock level, but isolation of SAO should be accomplished to confirm the diagnosis [38].

ELISA

ELISA test is designed for the specific detection of IgG. ELISA tests proved to be more sensitive than SAT and it offers the additional advantage to allow distinction between the early IgM response and later IgG response [4, 11, 25, 28]. Furthermore, ELISA can detect positive antibody levels for up to 10 months after abortion, suggesting that this test can be used for flock surveillance testing [11].

Serosurveillance in Switzerland and Spain indicated that, while the number of infected flocks may be high, some flocks may contain only a few seropositive sheep [1, 4].

Targeted and Scanning Surveillance: Control Measures

Salmonellosis by SAO is included in the OIE List of notifiable diseases, infections and infestations in force in 2021 (available at https://www.oie.int/en/what-we-do/animal-health-and-welfare/animal-diseases/?_tax_animal=terrestrials%2Csheep-and-goats&_tax_diseases=oie-listed), section "Sheep and goat". This means that the occurrence of outbreaks or also sporadic cases should be notified to veterinary authorities in countries where the disease has been found.

Epidemiologic data of the WAHIS database (see paragraph "Geographical distribution and epidemiology") originate from targeted and scanning surveillance, although in several countries no surveillance is specified. Thus, different levels of surveillance can be applied, according to the epidemiological situation. Targeted surveillance consists in the regular reporting of disease data by national institutions; it involves passive notification and it is not a very expensive method (https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/en/).

In targeted surveillance disease monitoring and control is accomplished through the identification of animals with bacterial vagial shedding or the direct detection of the responsible agent after abortions.

In contrast, scanning surveillance consists in the examination of all individuals with the scope to identify subclinically diseased animals. Additionally, the monitoring of a limited number of selected reporting sites is defined sentinel surveillance and, if carried out continuosly over time this system can provide with important data, useful to understand and follow disease trends in a geographic area. However, sentinel surveillance, being restricted to selected locations, may not be effective for detecting rarely occurring cases or affected individuals outside the catchment areas. (https://www.who.int/immunization/monitoring_surveillance/burden/VPDs/en/). For veterinary diseases, surveillance of sentinel units consists in the identification and control of one or more animals of known health or immune status in a defined geographical area to monitor the presence of infection. Sentinel units offer the possibility to target the surveillance depending on the estimated risk (i.e. introduction or re-emergence, cost or other practical issues), providing evidence of freedom from, or distribution of, disease [43].

In countries where the surveillance does not apply, there is the probability that infection prevalence is underestimated. A similar consideration has been made i.e., for Portugal [44].

The introduction of SAO epidemic strains in new areas is difficult to control due to the asymptomatic behaviors in infected adult lambs, rams, and nonpregnant ewes [8]. Since the infection is commonly introduced in a flock by a carrier sheep (usually asymptomatic), caution should be taken during animal movement and exportation, especially if coming from a flock with a history of past infection. SAO DNA presence for several months after abortion suggests that animals could be carriers for prolonged periods [2].

The particular epidemiologic scenario occurred in Switzerland some years ago raises some questions about monitoring methods. Although no abortions due to SAO had been reported for several decades before 2007, the results of seroprevalence survey of Wirz-Dittus et al. [4] showed that exposure to the agent (and resulting seroconversion) was endemic and that flocks with seropositive sheep could be found throughout the country, even though at a low average prevalence of 1.7%. The higher sensitivity of the serological assay suggests that a regular monitoring of seroprevalence could better reveal the epidemiological situation, with respect to culture based or only clinical investigations, especially for such notifiable disease. This is particularly true also in case of animals destined to exportation, for which a Veterinary Health Certificate for live export must be produced. However, since 1998 the OIE has the mandate to officially recognise disease-free areas of countries for trade purposes. Data are collected on a voluntary basis and apply to six diseases, among which salmonellosis by SAO is not included (https://www.oie.int/animal-health-in-the-world/official-disease-status, lastly accessed on July 2021).

In accordance with the provisions of the Terrestrial Animal Health Code (Terrestrial Code), OIE Members may wish to self-declare the freedom of their country, zone, or compartment from a disease. A Member wishing to publish its self-declaration for disease-freedom, should provide the relevant documented evidence of compliance with the provisions of the relevant chapters of the Codes. (https://www.oie.int/en/animal-health-in-the-world/self-declared-disease-status/). The OIE provides self-declarations published since 2000, but none of them regards SAO (https://www.oie.int/app/uploads/2021/05/eng-archive-2000-january-2021.pdf).

But also in case of implementation of an active surveillance system, the selection of animals to be subjected to serological control should be made according to reliable criteria, in a significative number, from representative geographic areas.

A last issue should be taken into account in the monitoring of SAO. The presence of SAO specific antibodies has been documented in wild ruminant populations, such as Spanish ibex (*Capra pyrenaica*), fallow deer (*Dama dama*), European mouflon (*Ovis aries*) and red deer (*Cervus elaphus*) from Southern Spain [45, 46]. Moreover, contact with other animals, such as birds and rodents has been documented as a risk for transmission [15]. More recently, [37] proved the absence of natural niches of SAO infection among other ruminant populations in Spain. However, the presence of chronic carriers among wild ruminants that might help to disperse this agent cannot be excluded.

Finally, the effective disease control can be obtained through annual vaccination with dead or live attenuated vaccines [5], which is particularly advisable in endemic areas [47]. Different anti-SAO vaccines has been developed. In particular, one vaccine with living SAO lacking *aroA* or *cya crp cdt* genes, or the virulence plasmid [25]. It has been reported that the last strain induced the highest level of immunogenicity.

More recently, the efficacy of a new inactivated vaccine has been assessed by García-Seco et al. [48], proving to be protective against paratyphoid abortion by SAO.

Conclusion

Taking into account the difficulties inherent to laboratory identification of SAO and the asymptomatic behaviors of some infected animals, pathogen presence can not be excluded also in countries not reporting salmonellosis by SAO for long periods.

Regular monitoring of pathogen circulation, especially through serological diagnosis, is advisable to prevent disease introduction and spread in SAO-free areas, especially in case of animal export, and to reduce abortion risk.

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