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Zoonotic risks of pathogens from sheep and their milk borne transmission

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ABSTRACT

Sheep were domesticated around 9000 BC in the Middle East, and since then milk from sheep gradually became very popular, not only for drinking but also for making cheeses and other dairy products. Nowadays, these dairy products are also important for people with an allergy to cow milk, and these products are an essential part of the local daily diet in regions of the world that are not suitable for cows and goats.

Consumption of raw milk and raw milk products has a zoonotic risk, and with regard to sheep, the main pathogens associated with such dairy products are: *Brucella melitensis*, *Campylobacter* spp., *Listeria* spp., *Salmonella* spp., Shiga-toxin producing *Escherichia coli*, *Staphylococcus aureus*, tick borne encephalitis virus, and *Toxoplasma gondii*. Especially, young children, elderly people, pregnant women and immunocompromised (YOPI) persons, and those suffering from disease should be aware of the risk of consuming raw milk and raw milk products. This latter risk can be reduced by proper flock health management, prevention of contamination during milking, adequate milk processing, transport, and refrigerated storage. Only processes equaling pasteurization sufficiently reduce zoonotic risks from milk and milk products, but proper cooling is essential and recontamination must be prevented. Therefore, strict hygiene practices throughout the production process and supply chain especially for raw milk and raw dairy products, should be applied. Small scale production systems pose a greater risk compared to industrialized production systems because of a less protocolized and controlled production process.

This manuscript describes zoonotic risks of pathogens from sheep and their milk borne transmission. Additionally, routes of contamination, possibilities for multiplication, and prevention measures thereof are described. We summarize some major human outbreaks caused by consumption of sheep milk and products made thereof, and finally discuss their implications.

1. Introduction

Nowadays, milk from sheep and products made from sheep milk are popular in many populations and areas. Furthermore, these products are consumed by people with allergies to cow milk. In ancient days, except for nomadic life and backyard farming, milk was collected from small farms with small numbers of animals, and milk and milk products were consumed mainly by those living nearby. In the early 1900's, urbanization level and the demand for dairy products increased, leading to industrialization of the dairy industry in more developed countries. In contrast with the dairy cattle industry, currently, milk production from sheep in many countries still takes place on a small scale and is of minor importance, volume wise (Ranadheera et al., 2018). However, sheep and goat milk have probably been used for a longer time by mankind than cow milk, as sheep and goats were domesticated from around 9000 BC in the Middle East, while cattle were domesticated more than a millennium later (Brandford Oltenacu, 2004).

In the EU, for example, sheep milk production nowadays represents only 1.8 % of the annual milk production, and production mainly (2011: 92 %) takes place in Greece, Spain, France, Italy, and Romania. Notably, two thirds of the world's sheep milk is produced in the Mediterranean area. In 2016, Europe produced 3.0 million tons of sheep milk, mainly used for the production of dairy products (Gonzales-Barron et al., 2017). Mostly, processing takes place at farm level, in small local dairies or in regionally operating cheese factories, often using raw milk (Gonzales-Barron et al., 2017). This small scale production results in a wide range of special products made from sheep milk that are mainly regionally consumed (Ranadheera et al., 2018).

Foodborne infections are responsible for millions of human illness

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cases each year, and the morbidity rate is higher in less developed countries. However, in developed countries, raw milk and raw milk products are nowadays widely promoted, by certain groups in the society, as healthy and more tasteful compared to heat treated milk, thus increasing health risks in countries with otherwise high health standards.

One of the oldest signs of foodborne infections in humans possibly caused by consumption of sheep milk was found by anthropological examination of skeletons of people who fled for the vulcanic eruption of Mount Vesuvius, 79 AD. Typical bone lesions of brucellosis were found in 17.4 % of adult victims. This was consistent with the presence of cocco-like forms that morphologically and dimensionally seemed to be *Brucella* spp., suggested to be linked to consumption of dairy products from sheep (Capasso, 2002).

The risk of milk borne infections has decreased during industrialization, because of the introduction of thermal processing of milk, standardization of production processes, good manufacturing and hygiene practices along the food supply chain, as well as the implementation of regulations. Nevertheless, as long as pathogenic microorganisms are present in raw milk, consumption of (raw) dairy products will remain a public health concern.

Zoonoses are infections that can spread from animal to man. Most zoonotic agents from small ruminants are transmitted by direct contact or through inhalation after becoming airborne. Also transmission by vectors can occur. Therefore, people with direct and indirect contact, like farmers, veterinarians and slaughterhouse personnel are at prime risk. However, transmission of pathogens from animals to humans can also occur via consumption of milk and meat, especially when these products are consumed raw (Ganter, 2015).

Ample research has been published on the risks associated with consumption of raw milk and products made thereof. However, mainly focusing on cow's milk, and only limited on sheep's milk. This review aims to describe zoonotic risks of pathogens from sheep and their milk borne transmission, possible effects on human health, and risks of antimicrobial resistant bacteria. Furthermore, we describe routes of contamination, possibilities for multiplication and prevalence of these pathogens in milk from sheep and products made thereof as well as measures to control these, and summarize and discuss the critical control points in this process.

2. Risks of zoonotic pathogens from sheep and their milk borne transmission

Milk is a natural product, secreted by the mammary gland of mammals. Milk is rich in proteins, lipids, and sugars, and contains some minerals and vitamins. Presence of micro-organisms, of which some may pose a risk to human health, is normal. Most pathogenic micro-organisms that can be present in milk are associated with more milk-producing animal species, such as bovines, small ruminants, horses, donkeys and camelids, but others are more specifically associated with a single species (EFSA BIOHAZ Panel, 2015). Some pathogens need to reach high numbers to cause disease in man, which makes illness caused by properly stored milk or milk products unlikely, as proper storage will prevent growth of most of these pathogens. However, some pathogens are able to grow at refrigerator temperatures, in which case a low initial microbiological load can result in life threatening loads even after properly storage. Furthermore, some other pathogens have a low infectious dose, thus growth is not necessary to cause infection in man.

Milk can get contaminated with micro-organisms in two ways: by endogenous or by exogenous transfer. In the former, micro-organisms are excreted with the milk; in the latter, they are introduced during or after milking either from the udder skin, from the environment (faeces, dust, apparatus, human, etc.), or during processing. In both cases, thermal treatment reduces the microbiological load of milk. Hygiene, both in the stable, during milking and at further processing can prevent or at least minimize exogenous contamination of milk and products made thereof (EFSA BIOHAZ Panel, 2015; Gonzales-Barron et al., 2017). In addition, hygiene in the stable and during milking reduces the transfer of pathogens from either the environment or infected animals to non-infected animals, thus also affecting the number of animals possibly excreting pathogens in the milk.

Table 1
Micro-organisms with zoonotic potential, associated with sheep and their possibly milk borne transmission.

Micro-organisms that may be present in sheep milk	
Bacteria	*Brucella* spp.
	Campylobacter spp.
	Coxiella burnetii
	Leptospira spp.
	Listeria spp.
	Salmonella spp.
	Shiga-toxin producing *Escherichia coli Staphylococcus aureus*
Fungi	Not known
Parasites	*Toxoplasma gondii*
Viruses	Rift Valley fever virus (RVFV)
	Tick borne encephalitis virus (TBEV)
Micro-organisms with minor risk of transmission via sheep milk	
Bacteria	*Bacillus anthracis*
	Bacillus cereus
	Chlamydia abortus
	Clostridium spp.
	Corynebacterium spp.
	Erysipelothrix rhusiopathiae
	Helicobacter spp.
	Mannheimia haemolytica
	Mycobacterium bovis
	Streptococcus spp.
	Yersinia spp.
Fungi	Several species (see Table 3)
Parasites	*Cryptosporidium* spp.
	Giardia duodenalis
Viruses	*Orf virus*
	Middle East respiratory syndrome coronavirus (MERS-CoV)

For this review, we distinguished between major and minor pathogens, based on expert opinions. This was done by discussing the combination of human incidence and severity of symptoms, from which the first one was leading factor. Major and minor pathogenic micro-organisms transmitted with milk and dairy can be divided in different groups (Table 1): 1) bacteria, like *Brucella melitensis*, pathogenic *Escherichia coli*, *Listeria* spp., and *Salmonella* spp. as most frequently described in sheep milk, 2) fungi, mainly causing bovine, but also described as cause of ovine mastitis, 3) parasites, with *Toxoplasma gondii* as main hazard, and 4) viruses that can be transmitted from sheep milk to humans like tick borne encephalitis virus (TBEV) and Rift Valley fever virus (RVFV).

In the following paragraphs, we describe the main zoonotic micro-organisms with relevance to public health that are possibly associated with sheep and elaborate on their threat to public health via consumption of raw sheep milk and products made thereof. Micro-organisms of supposed minor zoonotic risk via milk and dairy products are briefly described in Table 2 and 3.

2.1. Bacteria

2.1.1. Brucella spp

Brucella spp. are Gram-negative bacteria that cause brucellosis, one of the major zoonotic infections worldwide (Pappas et al., 2006). In sheep, *Brucella melitensis* is the most common cause of brucellosis, but *Brucella abortus* can also play a minor role in small ruminants (Ganter, 2015). Brucellosis in sheep causes economic losses as a consequence of abortion, fertility problems, decreased milk production, and increased costs of treatment. *B. melitensis* is still endemic in West and Central Asia, Africa, and Latin America. In Europe, *B. melitensis* is mainly present in Mediterranean countries. In Australian flocks, *B. melitensis* has never

Table 2
Bacteria associated with sheep and with minor zoonotic potential via milk or products made thereof.

Agent	Explanation of the possible risk for humans
Bacillus anthracis (spore forming Gram-positive rod)	Human cases are mainly associated with contact with slaughtered of dead or succumbing animals, but food infections (meat) are possible. Milk is not considered as a vehicle (AFSSA, 2008; EFSA BIOHAZ Panel, 2015).
Bacillus cereus (spore forming Gram-positive rod)	Contaminates milk via environment. Associated (in EU) with milk from bovine animals, donkeys and horses, not with milk from small ruminants (EFSA BIOHAZ Panel, 2015).
Chlamydia abortus (Gram negative)	Human cases mainly associated after direct or indirect contact with shedding sheep and goats in the periparturient period. The pathogen is not considered to be transmissible via milk (EFSA BIOHAZ Panel, 2015).
Clostridium spp. (spore forming anaerobic Gram-positive rod)	Several species have zoonotic potential. In milk or cheese, clostridial spores don't germinate and cells don't replicate. Numbers necessary to cause illness are not reached (Turchi et al., 2016; Drouin and Lafrenière, 2012). Milk is not considered as a vehicle (EFSA BIOHAZ Panel, 2015).
Corynebacterium spp. (Gram-positive rod)	Infection is mainly labor-related (cutaneous infection) (Peel et al., 1997). Milk is a very rare transmission route for *C. pseudotuberculosis* (Claeys et al., 2013).
Erysipelothrix rhusiopathiae (Gram-positive rod)	Humans are generally infected by direct contact with animals or animal products (Brooke and Riley, 1999). The pathogen is not considered to be transmissible via milk (EFSA BIOHAZ Panel, 2015).
Helicobacter spp. (Gram-negative spirochaete)	Cause gastric infections in humans. *H. pylori* is found in sheep milk (Verraes et al., 2014). The role as zoonotic agent is under debate. The pathogen is not considered to be transmissible via milk (EFSA BIOHAZ Panel, 2015).
Mycobacterium avium subsp. *paratuberculosis* (acid fast rod)	Suggested cause of Crohn's disease, however not conclusive (EFSA BIOHAZ Panel, 2013a). The zoonotic risk of this pathogen remains under debate. The pathogen is not considered to be transmissible via milk (EFSA BIOHAZ Panel, 2015).
Mycobacterium bovis (acid fast rod)	Mainly associated with cows. Experimentally infected sheep shed in milk (Keyhani, 1970). Raw milk or raw milk cheese are possible routes of transmission.
Streptococcus spp. (Gram-positive coccus)	For some pathogenic species, food is a known transmission route. Infections caused by consumption of raw milk and dairy products containing *S. equi* subs. *zooepidemicus* are rare and mainly related to cow milk (Barrett, 1986; EFSA BIOHAZ Panel, 2015; Eyre et al., 2010; Steward et al., 2017).
Yersinia spp. (Gram-negative rod)	Although *Y. enterocolitica* is present in sheep in Europe (Van Engelen et al., 2014), only *Y. pseudotuberculosis* is considered a hazard of low risk in Europe in relation to milk from small ruminants (EFSA BIOHAZ Panel, 2015).

been detected (FSANZ, 2009b).

In humans, *Brucella* spp. cause non-specific, mild clinical signs, or more severe and chronic symptoms. Four species of brucella are pathogenic to human, of which *B. abortus* and *B. melitensis* are associated with sheep. *B. melitensis* causes the most severe symptoms. In countries where brucellosis is not endemic, diagnosis may be delayed, resulting in a more severe course of the disease (RIVM, 2013). For humans, vaccines are not available (Ducrotoy et al., 2017), and treatment with antibiotics is difficult (El-Sayed and Awad, 2018).

Brucella spp. infected animals secrete the bacterium during and after parturition and abortion in genital fluids, and in milk, but contamination of milk may also occur from the environment (Claeys et al., 2013). *B. melitensis* does not grow under refrigerated conditions, but small numbers (10–100 bacteria) can cause disease in man (EFSA BIOHAZ Panel, 2015; El-Sayed and Awad, 2018). Prevalence of *Brucella* spp. in raw sheep milk will depend on the endemic status of a region, and can be as high as 46 % (FSANZ, 2009b). People get infected by *Brucella* spp. via contact with birth products of shedding animals and after consumption of contaminated animal products. Risk factors for brucellosis are working on a dairy farm, consumption of raw milk, home slaughtering of sheep, and working in a slaughterhouse (El-Metwally et al., 2011). Control of animal brucellosis, food hygiene measures and pasteurization of milk, known to adequately reduce *Brucella* spp. (Juffs and Deeth, 2007), are the appropriate methods to reduce the occurrence of this disease (Ducrotoy et al., 2017).

B. abortus is not considered by EFSA as a main hazard in sheep milk in the EU due to the low incidence of human cases. *B. melitensis*, however, is considered a main hazard due to the severity of the disease and the number of cases (EFSA BIOHAZ Panel, 2015).

Table 3
Non-bacterial agents associated with sheep with minor zoonotic potential via milk or products made thereof.

Agent		Explanation of the possible risk for humans
Fungi		
	Several species (such *Candida albicans*, *Candida krusei*, *Candida tropicalis, and Trichophyton verrucosum*)	In cattle, various pathogenic fungi can infect the udder and be exreted in milk. Of these species, only *Candida albicans* is considered a possible hazard in raw milk, but transmission via milk has not been reported. No information on the risk of fungi in sheep has been found. (Streinu-Cercel, 2012; Panelli et al., 2014; EFSA BIOHAZ Panel, 2015).
Parasites		
	Cryptosporidium spp.	Zoonotic potential differs per species. *Cryptosporidium parvum*, and *Cryptosporidium cervine*, might be relevant. Milk borne human cases are not described (FAVV, 2015). Therefore, although considered to be transmissible via milk, *Cryptosporidium* spp. are not considered as a hazard in sheep milk in Europe (EFSA BIOHAZ Panel, 2015).
	Giardia duodenalis	Immunocompromised or young individuals are at risk (Giangaspero et al., 2005). *G. duodenalis* consists of several assemblages which seem more or less host specific (Monis and Thompson, 2003). Milk borne human illnesses are not described. Raw milk and dairy are not considered a transmission route (EFSA BIOHAZ Panel, 2015).
Viruses		
	Orf virus	Causes skin lesions in humans and small ruminants. Lesions on the udder of small ruminants can be present. Nevertheless, direct contact is the main route of infection. The pathogen is not considered to be transmissible via milk (EFSA BIOHAZ Panel, 2015).
	Middle East respiratory syndrome coronavirus (MERS-CoV)	In humans, the course of infections can vary from asymptomatic to death (Miguel et al., 2015). Dromedary camels are strongly suspected to be the source of this zoonotic disease. Inoculation of sheep and goats did not result in shedding of MERS-CoV (Adney et al., 2016). Therefore, the possible role of MERS-CoV as zoonotic agent from sheep milk seems to be limited.

2.1.2. Campylobacter spp

Campylobacter spp. are Gram-negative curved bacteria and part of normal gut flora of many animal species, including dairy livestock, such as sheep (Horrocks et al., 2009). Several *Campylobacter* spp. have zoonotic potential, causing both mild (gastrointestinal disease) and severe symptoms (Guillain Barré syndrome) in man (Huang et al., 2015). *Campylobacter jejuni* and *Campylobacter coli* are the most frequently reported species causing foodborne disease (Horrocks et al., 2009). The infectious dose varies between 100 and 10,000 bacteria (FAVV, 2013; Juffs and Deeth, 2007; Verraes et al., 2014). But also *Campylobacter fetus* subsp. *fetus,* which causes abortion in sheep, is zoonotic (Huang et al., 2015).

Infection of animals with *Campylobacter* spp. occurs vertically or horizontally through faeces, and during abortion (Horrocks et al., 2009; Huang et al., 2015). Presence of *Campylobacter* spp. in milk is mainly caused by (in)direct faecal contamination (van Bokhorst-van de Veen et al., 2015), and indirect with *Campylobacter fetus* subsp. *fetus* after abortion (Huang et al., 2015).

Data reported to EFSA (2011–2015) show an overall prevalence of *Campylobacter* spp. in any type of milk of 0.6 %. Data on sheep milk are however scarce (EFSA and ECDC, 2013, 2014; EFSA and ECDC, 2015a, b; EFSA and ECDC, 2016). In a review, Verraes et al. (2014) only mentions one study in which *Campylobacter* spp. was detected in sheep milk, with a prevalence of 2.2 % (N = 90 samples). No additional data were available in the EFSA opinion on risks of raw drinking milk. A meta-analysis carried out by Christidis et al. (2016) on data available in North America, Europe and Oceania, showed a weighted mean prevalence of campylobacter in raw milk of any type of animal of 1.2 %. Regional and animal differences were noticeable; the highest prevalence was observed in the United Kingdom (6.4 %), and cow milk (1.3 %) more frequently contained campylobacter than milk from other animal species. For sheep milk, a prevalence of 1.1 % was estimated, based on five studies, including a total of only 135 samples from sheep.

Campylobacter spp. do not grow below 30 °C and numbers will decline slowly in milk during storage. Raw milk consumption is frequently associated with outbreaks of campylobacteriosis. Pasteurization is adequate to reduce the numbers of *Campylobacter* spp. in raw milk (Juffs and Deeth, 2007; EFSA BIOHAZ Panel, 2015; Huang et al., 2015).

Campylobacter spp. may survive during manufacturing of cheese (Christidis et al., 2016), which is confirmed by data of EFSA (2011–2015) that show an overall prevalence of *Campylobacter* spp. in cheeses of 0.2 %. For cheeses made from sheep milk, a prevalence of 1.3 % (n = 2) was reported for *C. jejuni*. Cheeses were made from raw or low heat-treated milk. Reviewing data on prevalence studies of *Campylobacter* spp. in cheeses and butter in general in Europe, however, did not reveal any positives (FAVV, 2015; Verraes et al., 2015). In raw sheep milk, *Campylobacter* spp. are considered a main hazard (EFSA BIOHAZ Panel, 2015), but also products made thereof are associated with campylobacteriosis.

2.1.3. Coxiella burnetii

Q fever is a zoonotic disease caused by the intracellular Gram-negative bacterium *Coxiella burnetii*. This pathogen is found worldwide, with the exception of New Zealand (Pires et al., 2017). Although this bacterium can be shed by other animal species like dogs, cats, birds and ticks, ruminants are the main animal reservoir of *C. burnetii*, which may cause reproductive disorders. After shedding, which mainly occurs in birth products after abortion, but also after normal parturition, *C. burnetii* contaminated aerosols are the main route of transmission to humans. Worldwide, several airborne outbreaks of Q fever have been related to shedding of *C. burnetii* by small ruminants (Van den Brom et al., 2015). In the Netherlands, a large Q fever outbreak with shedding dairy sheep and dairy goats as source caused illness in more than 4000 people. Serious complications of Q fever are known and even mortality has been described (Kouijzer et al., 2018).

In addition to this airborne route, a foodborne route may exist as *C. burnetii* can be excreted in milk from ruminants, and shedding in milk can persist for several months, for goats longer than for sheep. Despite this, the role of food in the transmission of *C. burnetii* to humans is still under debate (Verraes et al., 2015). Being an intracellular bacterium, *C. burnetii* does not grow in milk. *C. burnetii* is considered to be heat resistant, but the pasteurization process for milk is designed for a 5–6 logarithmic reduction in numbers of this specific pathogen (Juffs and Deeth, 2007; Pexara et al., 2018). Some publications suggest that Q fever outbreaks can be caused by consumption of raw milk (Gale et al., 2015; Pexara et al., 2018). These authors conclude that risk of *C. burnetii* infection through consumption of unpasteurized milk and milk products cannot be considered negligible but is low in comparison to transmission via inhalation of contaminated aerosols. Viable *C. burnetii* in cheese made from unpasteurized milk are rarely detected (Gale et al., 2015), but DNA from *C. burnetii* has been demonstrated by PCR in unpasteurized cheeses (Galiero et al., 2016). Outbreaks of coxiellosis caused by dairy products have not been described for Europe, USA and Canada (FAVV, 2015).

Therefore, it is not clear whether infection from raw milk and raw milk products will result in clinical Q fever (EFSA AHAW Panel, 2010; EFSA BIOHAZ Panel, 2015; Pexara et al., 2018).

2.1.4. Leptospira spp

Several species of the Gram-negative genus *Leptospira* are zoonotic, causing leptospirosis, a disease with a wide spectrum of symptoms in humans, ranging from mild infection to severe multi-organ infection syndromes with high mortality (Fratini et al., 2016). The disease is more common in tropical regions than in a moderate climate and the source of human infection is direct or indirect contact with urine of an infected animal. Infections are mainly acquired through occupational or recreational exposures. Dairy cattle and sheep are known as maintenance hosts of some *Leptospira* species and livestock farming is a major occupational risk factor worldwide. Dairy farming, especially milking, has the highest risk and is associated with the serovar Hardjo, that can also be present in sheep (Levett, 2001). However, sheep seem less susceptible to leptospirosis than other animal species (Bertelloni et al., 2017). The transmission of *Leptospira* spp. occurs through urine or other material from infected animals, water, soil or forages. Transmission to humans may occur through contaminated milk, following either direct excretion in milk (rarely) or urinal contamination of milk (Levett, 2001; Ganter, 2015). Nevertheless, milk is not regarded as a transmission route by EFSA (EFSA BIOHAZ Panel, 2015).

2.1.5. Listeria spp

The Gram-positive genus *Listeria* comprises a number of species, of which *Listeria monocytogenes* is the most relevant for human health (Rocha et al., 2017). An infection is typically foodborne (Buchanan et al., 2017), and may pass asymptomatically, or with mild gastroenteritis, or may result in severe outcomes with sepsis, meningitis and, for pregnant women, miscarriage or stillbirth (Rocha et al., 2017). The infective dose of *L. monocytogenes* is assumed to be > 1000 bacteria for the general population, but lower (10–100) for susceptible populations (FSANZ, 2009b). New data from EFSA suggest that this dose is generally higher, and that 90 % of the invasive cases of listeriosis are caused by food containing > 2000 CFU/g (EFSA BIOHAZ Panel et al., 2018).

Listeria spp. are ubiquitously present in the environment (Buchanan et al., 2017), which (e.g. feed and contaminated equipment) is the most important contamination source of milk, but direct contamination of milk by shedding animals also occurs (Gonzales-Barron et al., 2017; Jordan et al., 2016). If so, *L. monocytogenes* may be shed intermittently in high numbers in milk of infected animals (FAVV, 2015; Verraes et al., 2014). Shedding may continue for a long period, also in ewes not showing signs of disease (Gonzales-Barron et al., 2017; Schoder et al., 2011). Ewes with subclinical mastitis are a more important source of contamination than the environment (Condoleo et al., 2017), and in small flocks, one single ewe can have a large impact on *L.*

monocytogenes levels in bulk tank milk. In addition to risk factors as flock size, and feeding silage (Schoder et al., 2011), contamination prevalence may depend on the season, with a decreasing trend from start to end of season after lambing (Condoleo et al., 2017).

It is assumed in general, however, that milk is only contaminated with low numbers (0.01–10 cfu/L), which is based on data from cow milk (EFSA BIOHAZ Panel, 2015). In milk, *Listeria* spp. compete with the natural microbiota, and growth is therefore limited (Claeys et al., 2013). Cheese, however, and especially soft and semi-soft cheese, is an ideal medium for growth of *L. monocytogenes* (van Asselt et al., 2017), even more so, since this pathogen grows at low temperatures and shelf life of cheeses is relatively long. Using pasteurized milk for cheese making effectively reduces the number of *L. monocytogenes* present in cheese. However, this pathogen is frequently associated with recontamination events (Juffs and Deeth, 2007; Buchanan et al., 2017; van Asselt et al., 2017).

A meta-analysis of Gonzales-Barron et al. (2017) demonstrated goat milk cheeses significantly more often to contain *L. monocytogenes* (12.8 %; 7 studies) than sheep milk cheeses (3.6 %). Data reported to EFSA (2011–2015) show that for cheeses made from sheep milk, soft and semi-soft cheeses were most often contaminated (2.3 %), which is also the case for cow milk cheeses. Interestingly, hard (1.7 %) and fresh cheeses (2.0 %) made from sheep milk contain *L. monocytogenes* more frequently than cheeses made from cow milk (1.4 %). For hard cheeses made from sheep milk, 0.8 % exceeded the limit of 100 cfu/g. These data counterspeak the general opinion that hard cheeses do not pose such a great risk concerning *L. monocytogenes*, which is based on the fact that *L. monocytogenes* has a lesser ability to grow in hard cheeses (Buchanan et al., 2017; Lahou and Uyttendaele, 2017; van Asselt et al., 2017). However, in all cases, soft and semi-soft cheeses showed the highest number of samples exceeding the European Union limit of 100 cfu/g. Based on data presented, it seems fair to suggest that cheese made from sheep or goat milk pose a greater risk to the health of the consumer than cow milk cheese. Although *L. monocytogenes* is present in raw milk, it is not considered a main hazard in this product (EFSA BIOHAZ Panel, 2015). This pathogen is, however, a hazard in dairy products (EFSA BIOHAZ Panel et al., 2018).

2.1.6. Salmonella spp

Salmonella spp. are Gram-negative bacteria that belong to the family of *Enterobacteriaceae*. The genus is divided into two species, of which mainly serovars belonging to the group of *Salmonella enterica* subsp. *enterica* are associated with warm blooded animals and human disease. While *Salmonella* Enteritidis and *Salmonella* Typhimurium are serotypes that are most frequently reported to cause human foodborne illness, in essence all serotypes are pathogenic for humans (European Commission, 2003). Symptoms vary from mild (gastroenteritis) to severe (e.g. sepsis) and from acute to chronic (e.g. irritable bowel syndrome) (Steiner, 2013).

The main contamination route of milk with *Salmonella* spp. is via faeces or other material from the environment, although *Salmonella* spp. may be excreted directly in the milk by an infected animal (Claeys et al., 2013; van Asselt et al., 2017). *Salmonella* spp. will not grow in refrigerated milk (EFSA BIOHAZ Panel, 2015), nor in cheese. However, in cheese survival can extend for a long period (Alemdar and Aĝaoĝlu, 2010). Pasteurization of milk effectively inactivates *Salmonella* spp. serotypes (Juffs and Deeth, 2007).

The infectious dose depends on the serotype, but is estimated to be as low as one organism (FAVV, 2013) or between 10 and 100 (Juffs and Deeth, 2007), and thus very low concentrations in raw milk and cheese may already cause foodborne illness (van Bokhorst-van de Veen et al., 2015).

Data reported to EFSA (2011–2015) show an overall prevalence of *Salmonella* spp. in any type of milk (raw, pasteurized, cow, goat, sheep) of 0.1 %. Out of 47 recorded milk samples from sheep, two were positive (4.3 %). Data on prevalences of *Salmonella* spp. in sheep milk are scarce. The meta-analysis study of Gonzales-Barron et al. (2017) calculated an overall prevalence of 1.4 % (95 % confidence interval (CI): 0.3–6.6 %) in raw sheep milk, based on four studies.

Data of EFSA showed a prevalence of 0.2 % for *Salmonella* spp. in cheese in general, as well as in cheeses made from sheep milk. In their review on microbial hazards of raw milk dairy products (any dairy animal origin), Verraes et al. (2015) only found one study in which *Salmonella* spp. was detected in cheese. In this Portugese study, cheeses from milk of cow, goat and sheep were analysed (N = 70 samples), and the positives were (semi-)soft sheep milk cheeses (FAVV, 2015).

In raw sheep milk *Salmonella* spp. are considered a main hazard (EFSA BIOHAZ Panel, 2015), as is the case for products made thereof.

2.1.7. Shiga-toxin producing Escherichia coli

Escherichia coli are Gram-negative rods that belong to the family of *Enterobacteriaceae.* Traditionally, enteric *E. coli* have been divided into six pathotypes (Clements et al., 2012). Of these, isolates belonging Shiga-toxin producing *E. coli* (STEC) are of particular importance in the context of food safety. Illnesses associated with STEC range from mild to bloody diarrhoea, to haemorrhagic colitis and the haemolytic uraemic syndrome, and thrombocytopenia (EFSA BIOHAZ Panel, 2013b). The infective dose is low (< 10 bacteria) (FSANZ, 2009b). Ruminants, in particular cattle and sheep, are considered to be the main reservoir of STEC (FSANZ, 2009b; EFSA BIOHAZ Panel, 2013b). In a Dutch study among 24 dairy sheep farms, STEC was found on all of these farms (Opsteegh et al., 2018).

Contamination of milk with pathogenic *E. coli* occurs through faecal material present on teats and udder, or from the environment (EFSA BIOHAZ Panel, 2015). Also *E. coli* O157:H7, the major STEC serotype with regard to public health, can be present in raw milk from sheep (1%) (Verraes et al., 2014). A study from Caro et al. (2011) showed even a prevalence of 18 % for *E. coli* O157, 8% for *E. coli* O111, and 6% for *E. coli* O26. Mean levels (based on Most Probable Number (MPN)) for *E. coli* O157 and O111 were 0.22 and < 0.04 MPN/mL, respectively. The meta-analysis of Gonzales-Barron et al. (2017) on prevalence data of STEC in sheep milk shows an average prevalence of 4.8 % (95 % CI: 2.2–10.4 %; based on 8 studies), not different from the prevalence in goat milk but higher than in cow milk (1.8 %), as reported to EFSA (2011–2015). Data on sheep milk are hardly present in the EFSA database.

Data reported to EFSA (2011–2015) show an overall prevalence of STEC in cheeses made from sheep milk of 2.0 %. The meta-analysis of Gonzales-Barron et al. (2017) showed a difference in STEC prevalence between cheeses made from sheep milk (2.8 %; 5 studies) and goat milk (4.3 %; 13 studies). This study also showed that, although STEC was more prevalent in raw milk cheese from sheep or goat (10.0 %), STEC was also quite frequently present in pasteurized cheeses (4.7 %). As pasteurization effectively destroys pathogenic E. coli (Juffs and Deeth, 2007), this most likely is a result of processing failures or recontamination.

In raw sheep milk STEC is considered a main hazard (EFSA BIOHAZ Panel, 2015), as is the case for products made thereof.

2.1.8. Staphylococcus aureus

Staphylococcus aureus is a Gram-positive bacterium, and a main cause of mastitis in sheep (Macori et al., 2017). Spreading of an infection within a flock occurs through contact with milking equipment, contaminated bedding and milk (van Asselt et al., 2017). Milk can also get contaminated through milking equipment, the environment and milkers (Claeys et al., 2013). Monitoring of hygiene on sheep farms together with reduction of *S. aureus* are the main prevention measurements (Gonzales-Barron et al., 2017). *S. aureus* grows slowly in milk at 7 °C (EFSA BIOHAZ Panel, 2015).

S. aureus belongs to the group of coagulase-positive staphylococci, which are associated with human illness (van Bokhorst-van de Veen et al., 2015). Foodborne illness is caused by enterotoxins, known as staphylococcal enterotoxins (SET). Enterotoxins are only produced when sufficient numbers of *S. aureus* are present, are not produced at temperatures < 10 °C (van Bokhorst-van de Veen et al., 2015), and are heat stable (van Asselt et al., 2017). Although *S. aureus* is a fairly heat resistant vegetative micro-organism, pasteurization is considered effective in reducing numbers to an adequately low level (Juffs and Deeth, 2007).

Prevalence of *S. aureus* in raw sheep milk is estimated at 39.4 % (95 % CI: 22.7–58.9 %; based on 6 studies); no studies on *S. aureus* in sheep cheese are available. However, in goat milk, *S. aureus* is detected at a similar rate (35.2 %; 95 % CI 23.2–49.3 %, based on 19 studies) as in sheep milk, and for goat milk cheese the prevalence is 16 % (based on 21 studies) (Gonzales-Barron et al., 2017). Presence of *S. aureus* in dairy may also come from post-pasteurization contamination, poor hygiene and/or human error (Claeys et al., 2013).

Although raw milk is likely to be spoiled before *S. aureus* reaches numbers sufficiently high to produce enterotoxins in milk (Verraes et al., 2014), data reported to EFSA (2011–2015) show a prevalence of SET in milk of 1.4 % (N = 1109 samples). Only four samples were sheep milk, and all were negative. Although *S. aureus* and SET are present in and associated with outbreaks of raw drinking milk from cows, goats, sheep, horses and donkeys, it is not considered a main hazard in this product in the EU, based on incidence and/or severity of disease (EFSA BIOHAZ Panel, 2015).

In cheese, the above mentioned numbers necessary to produce SET can be reached due to initial high numbers already present in the raw milk or due to an insufficient start of the fermentation process allowing *S. aureus* to grow (van Asselt et al., 2017). Preventing foodborne problems caused by *S. aureus* starts with preventing mastitis and limiting growth in milk bulk tanks by temperature control (< 6 °C), in addition to pasteurization, rapid drop of pH, salt supplementation, proper fermentation during the cheese production process, and temperature control during further storage reduces the risk (van Bokhorst-van de Veen et al., 2015).

In Europe, a food safety criterion is set for SET in cheese. Levels of SET have to be determined when the number of coagulase-positive staphylococci in cheese exceeds the limit of 100.000 cfu/g. According to data reported to EFSA (2011–2015), SET was present in 2.5 % of the cheeses made from sheep milk. For cheeses made from cow milk and goats milk this is 0.5 % and 1.8 %, respectively.

In raw sheep milk *S. aureus* is not considered a main hazard (EFSA BIOHAZ Panel, 2015), but it is a hazard in products made thereof (FAVV, 2015).

2.1.9. *Mannheimia haemolytica*

Mannheimia haemolytica, a significant mastitis pathogen, can also be occasionally a potential zoonotic pathogen. Infection of people with this pathogen, transmitted from various animal sources, can lead, among others, to endocarditis, splenic abscessation (Takeda et al., 2003), and even fatal septicaemia (Punpanich and Srijuntongsiri, 2012). No milk borne transmission is described. The pathogen is not considered to be transmissible via milk (EFSA BIOHAZ Panel, 2015).

2.2. *Fungi*

In people, fungi can cause infection, particularly in those who are immunocompromised (Streinu-Cercel, 2012). In cattle, various pathogenic fungi can infect the udder and be excreted in milk, such as *Candida albicans*, *Candida krusei*, and *Candida tropicalis* (Dhanashekar et al., 2012). Of these species, only *C. albicans* is considered a possible hazard in raw milk, but as transmission via milk has not been reported, it is not considered a risk in raw milk (EFSA BIOHAZ Panel, 2015). Pathogenic fungi can survive moderate heat treatment. Total inactivation by heat can be established with a sufficient combination of temperature and duration. No information on the risk of fungi in sheep has been found. Therefore, sheep are not considered as a risk for fungal infections in humans after consumption of milk or milk products.

2.3. *Parasites*

2.3.1. *Toxoplasma gondii*

Toxoplasmosis is caused by the obligate intracellular parasite *Toxoplasma gondii.* In sheep and goats, *T. gondii* causes abortion, stillbirth, birth of weak lambs and fertility problems (Van Engelen et al., 2014). In humans, toxoplasmosis is mainly a risk when primary infection is acquired during pregnancy or in immunocompromised individuals. In other circumstances, infections are usually either asymptomatic or self-limiting (Deng et al., 2016; Belluco et al., 2017; Hussain et al., 2017). In the Netherlands and the USA, the disease burden estimates of this parasite are high (Hussain et al., 2017; Mangen et al., 2017).

Toxoplasma is a parasite with a sexual cycle in cats resulting in the production of oocysts, and an asexual cycle in a wide range of animal species including man. Cats are the key end host in the transmission cycle of this parasite and excrete oocysts in their faeces. Animals, such as sheep, get infected by ingestion of oocysts from e.g. water, grass or other feed that is contaminated with cat faeces. People, in addition, can get infected successively by ingestion of tissue cysts present in meat of infected animals or by ingestion of tachyzoites that are excreted in milk from animals suffering from acute toxoplasmosis (Deng et al., 2016). Ingestion by contaminated food is considered the main route of transmission for humans (Belluco et al., 2017; Boughattas, 2017).

Presence of (DNA of) *T. gondii* in milk from small ruminants has been described (Hussain et al., 2017), also in milk from sheep specifically (Camossi et al., 2011; de Santana Rocha et al., 2015; Fusco et al., 2007; Luptakova et al., 2015). Tachyzoites can survive at least several days in milk (EFSA BIOHAZ Panel, 2015). Furthermore, illness has been reported due to consumption of raw goat milk (Deng et al., 2016), and *T. gondii* does survive the processing of fresh cheese. However, in a systematic review on the risk of toxoplasmosis from food consumption, unpasteurized milk has been considered as unimportant (Belluco et al., 2017). This may be explained by the fact that tachyzoites are more sensitive to environmental conditions than tissue cysts and oocysts, (FSANZ, 2014). A meta-analysis on the milk-borne infection route of humans by Boughattas (2017) showed that risk factors for the milk borne infection route of *T. gondii* are consumption of goat milk and milk products, being immunocompromised, and living in North America, Middle East, and Latin territories. Also EFSA mentioned that most reported cases of toxoplasmosis acquired through the consumption of raw milk are from outside Europe (EFSA BIOHAZ Panel, 2015).

2.4. *Viruses*

2.4.1. *Rift valley fever virus*

Rift Valley fever (RVF) is an arboviral zoonotic disease which affects animals like cattle, sheep and goats, as well as humans. Infections caused by RVF virus (RVFV) have been reported at least since the 1930's in Africa and the Arabian Peninsula (Nicholas et al., 2014). In humans, infections mostly remain asymptomatic, however a significant number of infected people develop severe disease which includes haemorrhage, encephalitis, visual disturbances, and even occurrence of death (Ng'ang'a et al., 2016); RVFV is considered a major pathogen.

RVFV can spread by bites of mosquitos, but also by contact with infected animals and their products or tissues. Risk factors to acquire RVF are gender, contact with birthing animals, slaughtering and skinning of animals, and possibly drinking of raw milk (Nicholas et al., 2014). Pasteurization of milk decreases the risk of RVFV transmission to humans. Trade in small ruminants and their products plays an important role in spreading diseases such as RVF (Sherman, 2011).

Although, RVFV is excreted in the milk by infected animals (Claeys et al., 2013), transmission via milk is not considered important (OIE, 2009; EFSA BIOHAZ Panel, 2015).

2.4.2. Tick-borne encephalitis virus

Tick-borne encephalitis virus (TBEV) belongs to the genus *Flavivirus*, and is divided into three subtypes. The subtype which is endemic in Central and Western Europe is causing relatively mild symptoms in humans compared to the Siberian and Far-Eastern subtypes (Bogovic and Strle, 2015). Although TBEV is mainly transmitted from animals to humans via tick bites, transmission also occurs via consumption of raw milk and dairy products. TBEV is excreted in the milk by infected animals (Claeys et al., 2013). Symptoms seem to occur more frequently when the virus is transmitted through ingestion via food, than after transmission by tick bites (Dobler et al., 2012). TBEV is killed during pasteurization, and TBE in humans can be prevented by vaccination (Bogovic and Strle, 2015; EFSA BIOHAZ Panel, 2015; Offerdahl et al., 2016). Foodborne TBE outbreaks in Europe mainly occur after consumption of raw milk and dairy products from goats, followed by raw milk and dairy products from cows, but also cases after consumption of raw sheep milk and cheese have been described (Dobler et al., 2012; Grešíková et al., 1975; Kriz et al., 2009; Labuda et al., 2002; Zeman et al., 2004). Only one study, conducted in Poland, describes prevalence data for TBEV in raw milk, which involved screening raw milk from cows (11.1 % of 63 samples), sheep (22.2 % of 27 samples) and goats (20.7 % of 29 samples) (Cisak et al., 2010; EFSA BIOHAZ Panel, 2015). TBEV remains stable in refrigerated milk, but is inactivated during pasteurization (Offerdahl et al., 2016). In Europe, raw milk and dairy products from small ruminants are considered a main hazard for TBEV infection (EFSA BIOHAZ Panel, 2015).

3. Antibiotic resistance

Antibiotic resistance is a growing threat to both human and animal health, primarily through an increased risk of treatment failures. Bacteria can become resistant to antibiotics by mutations in genes associated with the mechanism of action of the compound or by acquisition of foreign DNA coding for resistance determinants through horizontal gene transfer. These processes occur independently of the use of antibiotics. However, once a resistant mutant emerges, used antibiotics eliminate the susceptible population and resistant bacteria will predominate (Munita and Arias, 2015). Therefore, resistant bacteria nowadays are more frequently seen as a consequence of the use of antibiotics than in the pre-antibiotic era (Ungemach et al., 2006; De Neeling et al., 2007; Scott and Menzies, 2011).

Several studies have been published on antibiotic resistant bacteria in sheep milk, both in milk from individual sheep, and in bulk milk, and also in raw sheep milk cheese. Studies were focused on resistant zoonotic bacteria, commensal bacteria, mastitis-causing bacteria, and specific resistances, including methicillin-resistant S. *aureus* (MRSA), extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria, and vancomycin-resistant enterococci (VRE) (Abdalhamed et al., 2018; Abo-Shama, 2014; Alian et al., 2012; Ariza-Miguel et al., 2014; Azara et al., 2017; Burriel, 1997; Carfora et al., 2016; Ceniti et al., 2017; Corrente et al., 2003; Giacinti et al., 2017; Jiménez et al., 2013; Lollai et al., 2016; Macori et al., 2017; Mousavi et al., 2014; Obaidat et al., 2018; Onni et al., 2011; Ortigosa et al., 2008; Sanciu et al., 2012; Solomakos et al., 2009; Spanu et al., 2012, 2014). Comparing literature data on antibiotic resistant bacteria in raw sheep milk is complicated because of several differences, e.q. in methodologies used to detect resistant bacteria, in determining susceptibility of bacterial isolates, in antibiotics in the test panel, and in interpretation criteria used to categorize isolates as susceptible or resistant. Additionally, differences between countries probably largely relate to farm management regarding hygiene and storage of milk, prevalence of resistant bacteria in sheep and farm environment, and policy of antibiotic use.

In December 2008, the Dutch government and farming industry agreed to reduce the use of antimicrobials in farm animals (LNV, 2008). At the end of 2018, a reduction of more than 63 % had been achieved compared to 2009, and almost no antibiotics that are important in treating infections in humans have been used for animals in recent years (MARAN,2018; NethMap, 2019). The aim for the remaining period ending ultimately 2020 is another reduction of more than ten per cent, making a total reduction of at least 75 % per cent in a period of twelve years. During this journey, several hurdles were taken step by step, for example, by improving stable climate, management and use of vaccinations. Together with a reduction in antibiotic use, a slight reduction in resistance appeared (NethMap, 2019).

Although the use of antibiotics in small ruminants in the Netherlands was low compared to other farm animals like pigs, poultry and cattle, and accordingly it is likely that small ruminants only play a minor role in the development of antibiotic resistance in the entire livestock industry (Santman-Berends et al., 2014), raw sheep milk may contain antibiotic resistant bacteria, including multidrug resistant bacteria. Raw milk and raw milk products can therefore act as a source for bacteria that are resistant to different groups of antimicrobials, potentially constituting a health risk for consumers.

The principles of controlling resistance development in bacteria present in sheep milk involve infection control at herd level and prudent use of antibiotics. The risk for human health can significantly be reduced by heat treatment of raw milk, and there are no indications that antibiotic resistant strains are more resistant to heat treatment than susceptible strains.

4. Human outbreaks of disease caused by sheep milk

In the EU, EFSA annually collects data on foodborne outbreaks from member states. Distinction is made between strong evidence outbreaks in which the association between causative agent, the implicated food vehicle and the patient is based on strong epidemiological or microbiological evidence, and weak evidence outbreaks in which this is not the case. In the period 2011–2016, a total number of 3736 strong evidence foodborne outbreaks were reported to EFSA. Dairy was involved in 6.2 % (231 outbreaks) of these outbreaks. Milk was the implicated food vehicle in 70 of these outbreaks, cheese in 129, and other dairy products in the remaining 32 outbreaks.

The most frequently reported causal agent of dairy based strong evidence outbreaks in the EU was *Salmonella* spp., followed by staphylococcal enterotoxin (SET), and *Campylobacter* spp. Other agents involved were pathogenic *E. coli*, flavivirus, *Bacillus* spp. (mainly *Bacillus cereus*), calicivirus (mainly norovirus), *Listeria* spp., *B. melitensis*, *Clostridium* spp. (*Clostridium perfringens*), *Yersinia* spp., and *Cryptosporidium parvum*. In some outbreaks, the causal agent was unknown. Most outbreaks were associated with cheese and milk. Milk borne outbreaks were mainly caused by *Campylobacter* spp. (56 %), flavivirus (11 %), *S. aureus*/SET (10 %), *Salmonella* spp., and STEC (both 7%), while *Salmonella* spp. (52 %) and *S. aureus*/SET (30 %) were the main reported hazards in cheese related outbreaks.

Information on the animal source was available in only 32 outbreaks. Cow milk or cheese was involved in 12 of those outbreaks, sheep milk or products made thereof in 11 cases, and goat milk or products made thereof in 10 cases. From the remaining 196 it was not known from which dairy species the milk originated. Pathogens associated with those outbreaks in which sheep milk or cheese made from sheep milk was involved were SET (7), *Salmonella* spp. (2), *Campylobacter* spp., and TBEV (both 1). In a risk assessment on raw drinking milk, EFSA mentioned that 27 strong evidence outbreaks involving raw milk were reported to EFSA in the period 2007–2012 (EFSA BIOHAZ Panel, 2015). None of these involved sheep milk or products made thereof. Based on data reported to EFSA, two outbreaks occurred in 2011 caused by SET in cheese made from sheep milk, and from 2007 to 2016, only eleven outbreaks were reported caused by consumption of sheep milk and products made thereof. One of the reasons for these few reported outbreaks could be the limited consumption of raw drinking milk from sheep in Europe (EFSA BIOHAZ Panel, 2015). The same conclusion was made by Verraes et al. (2014) who did not find any outbreak described in literature attributed to sheep milk.

The only reported outbreak to EFSA of campylobacteriosis by sheep milk and products made thereof during 2011–2015 took place in the Netherlands and was caused by *Campylobacter fetus* in fresh cheese, a rather uncommon species (Koppenaal, 2017).

In their risk assessment study, EFSA BIOHAZ Panel (2015) conducted an additional search on raw drinking milk associated outbreaks caused by TBEV which did not reveal any outbreaks related to sheep milk; mainly (raw) goat milk is mentioned as implicated food vehicle (Kriz et al., 2009). It should be noted that TBEV is endemic in many European countries and most human infections are caused by tick bites.

In Europe, milk borne outbreaks of *Brucella* spp. are not common anymore as many countries are free from brucellosis (OIE, 2009), and only a few outbreaks of human brucellosis caused by *B. melitensis* have been described in which sheep milk or milk products were involved (Karagiannis et al., 2012). It is assumed that in European countries where brucellosis is endemic, the foodborne risk of brucellosis is mostly related to consumption of raw milk from goats and sheep and products made thereof (Verraes et al., 2015). In an epidemiological study in a specific Greek endemic region during 2003–2005, it was shown that raw milk or cheese from goats or sheep was the route of infection in only 8.5 % of the cases; animal contact being the major route of infection (Minas et al., 2007).

An overview of reported outbreaks in the United States of America (USA) is available via the online National Outbreak Reporting System of the Centers for Disease Control and Prevention (CDC, 2017). During 1998–2016, 19,991 foodborne outbreaks were reported, and only 190 were caused by milk (1.0 %), and 98 by cheese (0.5 %). Milk borne outbreaks were mainly caused by *Campylobacter* spp., STEC, and *Salmonella* spp. Other causal agents were *Cryptosporidium parvum*, *L. monocytogenes*, *Yersinia enterocolitica,* and *S. aureus*, other (single) bacteria, multiple bacteria, unknown or chemical. Similar to milk borne outbreaks, most cheese related outbreaks were caused by *Campylobacter* spp., followed by *Salmonella* spp., *L. monocytogenes*, norovirus, STEC, *Brucella* spp., *S. aureus*, *Shigella* spp., and other/unknown. Remarkable is the high contribution of *Campylobacter* spp. in cheese related outbreaks, as compared to the EU.

Information on the type of dairy animal is hardly available, and if so, none of the outbreaks involved sheep milk or cheeses made thereof.

In a non-exhaustive list of outbreaks in Europe, the United States of America and Canada, due to consumption of dairy products produced by Verraes et al. (2015), only two of the 64 outbreaks were associated with sheep milk dairy products, both caused by *S. aureus* enterotoxins. An overview of global outbreaks attributed to cheese (1973–2006) produced by FSANZ (2009b) listing 84 outbreaks, included only four outbreaks caused by sheep milk cheese (2 *S. aureus*, 1 *Campylobacter* spp., 1 *Shigella* spp.) and 16 by goat milk cheese. The sheep milk cheese outbreaks all occurred in Europe, those involving goat milk cheeses in all regions (Europe, USA, Canada and other). It must be noted, however, that in Australia, raw milk cheeses were not produced (FSANZ, 2009a and 2009b).

In New Zealand, 21 outbreaks were linked to the consumption of raw milk in the period from 2006 to 2013 (MPI, 2013). As the consumption of sheep milk is negligible in New Zealand, this type of product was not taken into consideration in the microbiological risk assessment associated with the consumption of raw milk, and no data are available on sheep milk (MPI, 2013).

5. Preventing animal infection, product contamination and bacterial growth

Milk and dairy products made from milk are complex natural products (Raynal-Ljutovac et al., 2008), and contamination can occur at different stages of production, processing and storage (Fig. 1). This means that handling these products from farm to fork should be carried out with care and awareness of the risks (Leedom, 2006).

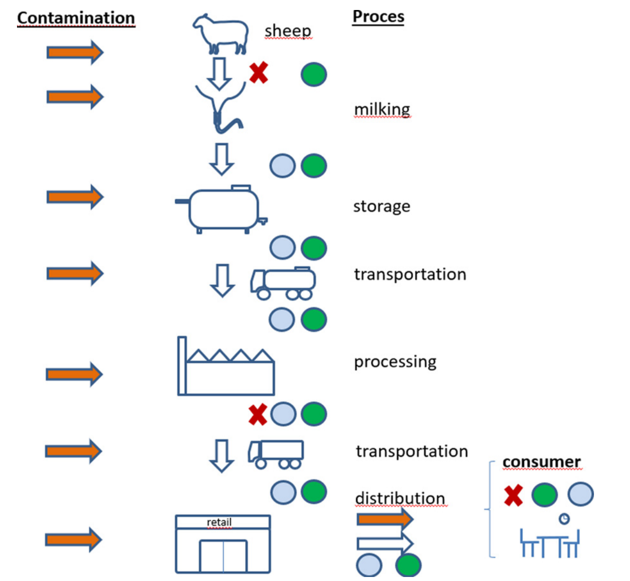

Fig. 1. Schematic overview of the dairy supply chain from farm to fork (consumer), showing possible entry points of pathogens (contamination: orange arrows) and control measures (blue dots: low temperature; green dots: hygiene; red crosses: eradication programs and pathogen reduction treatments of milk (e.g. pasteurization)). In cases where processing and retail take place on the dairy sheep farm, almost the same is applicable (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Several pathogens pose a risk to human health in relation to consumption of raw sheep milk or sheep milk products. Hygiene is important to prevent contamination, either when sheep are infected or when contamination occurs during processing of milk (Willis et al., 2018), but hygiene alone will not be enough to control pathogens. Eradication programs, for example for *B. melitensis* (Blasco, 2010), improve not only herd health but will also prevent zoonosis in humans (Fouskis et al., 2018).

After eradication of diseases from a herd or a country, monitoring of the disease status should be encouraged as part of the quality control system. Monitoring can be done in several ways, either by blood or bulk milk testing, and should be performed on a regular base. Proper identification of animals and registration of animal movements, preferably in a central database (Santman-Berends et al., 2016), is needed in combination with quarantine and testing of animals before they enter the flock as standard procedure on dairy sheep farms.

Eradication programs in combination with monitoring health status works for some pathogens like *B. melitensis*. However, for many pathogens, eradication programs are not available yet (Ganter, 2015). Therefore, hygiene in the barn, during milking and milk processing is the most effective route to prevent or reduce contamination of milk. For example for *Salmonella* spp. and *Campylobacter* spp., spreading through faeces in the bedding (Hutchison et al., 2005), resulting in dirty teats, or during milking can result in contamination of the milk; for these pathogens clean bedding and application of a high hygiene standard during milking are important.

Besides the above mentioned ways of contaminating milk, some pathogens like *S. aureus* and *L. monocytogenes* are excreted in milk and can infect other sheep (Gelasakis et al., 2015). Contamination of milk could occur during milking but also via the bedding in situations where ewes are leaking milk. Prevention of milk-milk contamination can be done by milking infected animals in separate groups, providing clean bedding, giving attention to hygiene during milking or by culling infected animals while vaccinating naïve animals.

Silage can play an important role in *Listeria* spp. (Wagner et al.,

2005) and *Clostridium* spp. infections. One of the ways to prevent contamination of milk is to prevent the presence of soil into silage, and proper conservation and storage of silage (Driehuis et al., 2018).

As many of the pathogens in milk can cause mastitis in sheep, mastitis should be considered as a zoonotic risk (Abebe et al., 2016; Botelho et al., 2018). Therefore, mastitis prevention measures are to a large extent also measures to prevent zoonotic infections through consumption of milk with pathogens.

The composition of milk makes it a suitable product for survival and growth of a wide range of pathogens during milking, processing and storage. In general, cooling reduces the proliferation rate of bacteria but some of them, like *Listeria* spp., are still able to multiply under refrigerator conditions. After milking, excellent temperature control throughout the whole food supply chain and at home should be assured in order to minimize growth of pathogenic bacteria and production of toxins (Porcellato et al., 2018).

To make milk safe for human consumption, heat treatment is the golden standard. Other techniques are either not allowed or not used. However, recently cold-pressed (pascalized) milk became available on the Australian market (NSW Food Authority, 2016; NVWA BuRO, 2017). The world-wide standard for pasteurization, according to the International Dairy Federation, is either a ‘low-temperature-long-time’ treatment (at least 63 °C for 30 min; batch pasteurization) or a ‘high-temperature-short-time’ treatment (at least 15 s at 72 °C), or treatments with an equivalent effect (Juffs and Deeth, 2007). These treatments effectively reduce the level of pathogenic bacteria present in milk. Sterilization of milk needs an ultra-high temperature treatment (UHT), a short time at least at 135 °C, which ensures a microbiologically stable product when stored at 30 °C for 15 days or for 7 days at 55 °C (in closed containers).

Furthermore, thermization is used, a sub-pasteurization process, conducted at temperatures ranging between 57 and 68 °C lasting for a short time (10–20 seconds). It is applied to extend the storage life of raw milk before normal pasteurization, by controlling the psychrotrophic bacteria. Thermization results in a 3–4 log reduction of the commensal microbiota of milk and is not designed to inactivate all vegetative pathogens present. In addition, it is used in the production process of certain types of cheese, to reduce the bacterial load, but without disadvantages for cheese ripening and whey protein degradation (Claeys et al., 2013; Juffs and Deeth, 2007).

6. Considerations

Milk from sheep is very popular in certain populations and areas. Taste and high fat content of cheeses from sheep milk make it popular. Nowadays, these dairy products are also important for people with an allergy to cow milk, and these products are an essential part of the local daily diet in regions of the world that are not suitable for cows and goats.

Healthy animals are the starting point for the production of safe and healthy food, but it should be kept in mind that several pathogens can be shed by animals not showing any signs of illness. Also in many cases of high somatic cell counts found in milk, no clinical signs of disease are seen. This indicates the need for a control plan for subclinical mastitis.

Raw milk does contain micro-organisms, and some of them pose a health risk to humans. Factors that impact the level of contamination of raw milk include animal-related factors like general animal health, herd size, age and production status, environment-related factors like housing, faeces, feed, soil, and water, and factors related to milking and operation of milking equipment (FSANZ, 2009b). Production and processing of milk from sheep is often performed under less stringent hygiene and quality control regulations compared to that from cattle. Several factors are described as possible reasons for this difference, like lower production per head, milking system, flock management, and wide geographic spread of production (Klinger and Rosenthal, 1997). Furthermore, it is suggested by Gonzales-Barron et al. (2017) that for goat milk cheeses, which are mainly produced in regions of the Mediterranean and Middle East, the higher levels of pathogens associated with this type of cheeses, compared to milk and milk products from sheep, may arise from the more artisanal production system. The same may be true for sheep milk cheeses compared to cow milk cheeses. Overall, these authors showed that pathogens are more prevalent in cheese made from goat milk compared to that from sheep (9,6 %–2,5 %) (Gonzales-Barron et al., 2017). This is however not reflected in the data reported to EFSA (2011–2015) that show a pathogen prevalence in cheeses made from cow, goat and sheep milk of 0.9 %, 1.1 %, and 1.3 %, respectively. However, prevalence of pathogens in milk is higher for sheep (7.7 %) and goat (3.7 %) than for cow (1.0 %). In the risk assessment carried out by Juffs and Deeth (2007) for the Australian situation, contamination of raw milk from sheep was considered to occur more frequently than contamination of cow and goat milk with regard to presence of STEC and *L. monocytogenes*, and less frequently with regard to *C. jejuni* and *Salmonella* spp. *S. aureus* was considered to be more prevalent in goat milk than in either cow or sheep milk.

As milk from small ruminants may be used more often for on farm production of cheese, compared to cow milk, the prevalence of pathogens will strongly depend on the health status of the herd and the food hygiene practices of the farmer. Stringent hygiene measures during milking are essential to prevent cross contamination between animals during milking. Furthermore, good hygienic practices throughout the entire production process are important to safeguard the health of dairy consumers. Presence of *S. aureus* in cheese from both raw and pasteurized milk has been described as an indicator of low hygiene during milking and processing (Gonzales-Barron et al., 2017).

Heat treatment of milk results in a reduction of the number of micro-organisms. The thermal death point differs for different micro-organisms. Duration as well as temperature influence survival rates of pathogenic micro-organisms during heat treatment. With increasing temperature, duration can be decreased to have the same results (Dhanashekar et al., 2012). Thermization treatment will not only have a positive effect by controlling spoilage micro-organisms and to some extend pathogenic micro-organisms, it also reduces lactic acid bacteria numbers and the biodiversity of raw milk bacteria in general. This inactivation of lactic acid bacteria might enhance the growth ability of potentially pathogenic enterococci (Samelis et al., 2009).

It is important to realize that in outbreaks caused by *L. monocytogenes*, it is quite difficult to identify the source, as the incubation period of listeriosis is fairly long, and can be up to many weeks. Thus, although *L. monocytogenes* is considered a main hazard in dairy products, the number of strong evidence outbreaks is limited.

Additionally, contamination of milk with veterinary drug residues can affect human health. Therefore, milk and milk products must be free from residues.

Several micro-organisms causing disease in small ruminants have zoonotic potential, especially many of those causing abortion (Van den Brom et al., 2012; Van Engelen et al., 2014). Some of them are not known as causing foodborne disease as is for example the case with *Chlamydia abortus*, which is able to infect humans after direct or indirect contact. Therefore, persons who work with small ruminants should be aware of these zoonoses as well.

Consumption of raw milk and products made thereof will always pose a risk. Therefore, stringent hygiene measures in combination with periodic control of these products should be applied.

7. Conclusion

Consumption of raw sheep milk and raw milk products made thereof can pose a zoonotic risk, although the registered number of confirmed cases is low. This risk can be further reduced by proper flock health management, prevention of contamination during milking and adequate milk processing, transport and storage. In the dairy industry, much knowledge is present about these risks, and how to control them.

In small scale production systems of sheep milk and dairy products, a higher risk remains compared to industrialized production because of a less protocolled and controlled production process. Especially the so called YOPIs - young children, elderly people, pregnant women, and immunocompromised persons - and those suffering from disease should be aware of the risk of consuming raw sheep milk and raw sheep milk products. Pasteurization, and similar or stronger processes, adequately reduces zoonotic risks of sheep milk and products made thereof, but preventing recontamination and proper cooling throughout the supply chain and at home are essential to keep these products safe.

Declaration of Competing Interest

All authors declare not to have a conflict of interest.

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