

Therapeutic gaps in the small ruminant segment

Meeting of 16/04/21

Participants: F. Guillaume (GDS Bretagne, representing GDS France and Race de France), J. Visse (Lacaune practitioner, representative of the SNGTV sheep commission), S. Blain (practitioner in Touraine, representative of the caprine commission), C. Hugnet (practitioner in the Drôme, representative of the CSMV), C. Paraud (Anses Niort)
for ANMV: JP Orand, L Baduel, S Barreteau, N Bridoux, C Miras, J. Bietrix, L. Fabry

Pathology	Problem* encountered *Economic: E / Cascade: C / Other: A	Problem only in the milk sector	Type of problem * (E/C/A)	Alternatives identified	No therapeutic solution identified	PRIORITIES	
						Major: M	minor: m
						Sheep	Goats
Digestive strongylosis, with increased resistance to benzimidazoles, levamisole and eprinomectin	<p>Feedback from the field of lack of efficacy of benzimidazoles, levamisole and eprinomectin (and not only when pour-on). Questionable relevance of the pour-on route, especially in sheep and goats, as it does not allow targeted treatment (licking). In addition, the pharmacokinetic properties are very heterogeneous. Risk also for the user's safety.</p> <p>In sheep: The majority of breeders administer orally the pour-on presentation of eprinomectin (also in goats), with a milk withdrawal period (WP) of 0 days instead of the 7 fixed days. Problem especially in Pyrenees where treatments are more frequent.</p> <p>EPRIBELE project: usage survey on the use of eprinomectin and field test in 6 goat farms to evaluate a method for detecting cases of lack of efficacy of the pour-on (see thesis and JNGTV 2020 communication).</p> <p>=> Almost exclusively off-label use of the pour-on formulation: via oral route and with variable doses leading to an increased risk of emergence of resistance.</p> <p>=> Lack of efficacy of the pour-on ± injectable eprinomectin (resistance?) highlighted in 4 out of 6 goat farms.</p> <p>=> Increase in PhV declarations with, to date, 18 declarations of lack of efficacy in sheep and 18 in goats.</p> <p>Knowing these risks of resistance and the exclusive possibility of the use of eprinomectin in dairy sectors, why new marketing authorisations are still granted for pour-on presentations?</p> <p>More pharmacovigilance data are needed to challenge marketing authorisations.</p>		A, C and E	<p>Eprinomectin solution for injection (EPRECIS) has a marketing authorisation (MA) extended to sheep and goats since November 2020. Interesting only when there is no resistance to eprinomectin.</p> <p>ZOLVIX (monepantel-based drug, anthelmintic of the amino-acetonitrile derivatives family effective against nematodes resistant to other classes of anthelmintics). To be able to use it in the dairy sector (MRL exists for milk), a residue study is needed to define a milk withdrawal period (WP). This alternative to benzimidazoles and ivermectin would be interesting, even if the treatment could be administered only at dry-off and/or during dry periods. Indeed, the dry period is long, particularly for sheep (5 months + 28 days of non-marketing of milk). In goats, the dry period is shorter (about 2 months) with 7 days of milk withdrawal. The cost of treatment remains high. 25-30% resistance to benzimidazoles is reported. The need for alternatives is therefore urgent in goats and sheep (Pyrenees in particular).</p>		n°1	n°1

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	<p>Monepantel (ZOLVIX), which belongs to another family, has a marketing authorisation (MA) only for sheep and, despite milk MRL, should not be used in milk-producing animals intended for human consumption. Indeed, the absence of a depletion study and a 35-day milk WP for the product's MA in New Zealand do not allow the cascade to be applied with a fixed 7 days WP without risk for the consumer.</p>						
Cryptosporidiosis	<p>Goats: safety concerns with halofuginone: it is rather a dose problem on goat kids because the product is suitable for cattle - Administration difficulties. Paromomycin satisfactory.</p> <p>Sheep: paromomycin: abomasal ulcers at twice the dose (i.e. 100 mg/kg), every 2 days, for 7 days. 1x dose would be sufficient to resolve clinical signs in most cases.</p> <p>First pathology but over-diagnosed: not necessarily linked to clinical signs. 50% prevalence in sheep herds with "criminals association" of <i>E. coli</i> and <i>Cryptosporidium</i>. Diarrhea at 4-8 days, tenesmus and colics, immunochromatography test (speed V-Diar 4) in 10 minutes (many false positives, overdiagnosis). Disinfection is difficult because carried by mothers.</p>		A	<p>Paromomycin sulphate (Parofor®) in the context of the cascade is widely used in sheep and goats, good efficacy reported.</p> <p>Halofuginone authorised in cattle can be used in the context of the cascade (different species, same indication).</p> <p>Reporting of alternative products on the market: Kryptophyt (food additive with Yucca extract) and Multigen (oral immunoglobulin). Reinforcement of the intestinal flora (lactic acid bacteria). Phytotherapy: how effective?</p>		n°2	n°5
Neonatal colibacillosis	<p>IMOCOLIBOV efficacy depends on the strains involved in goats and sheep (and according to passive immunity acquired via colostrum). Random availability from distributors. Lack of information on possible <i>E. Coli</i> serotypes responsible for septicemic, diarrheal, soft lamb, drooling lamb.</p> <p>Problem of non-typable serotypes. Lack of feedback on field use (only sharing info from users). Auto-vaccines: very long production (10 weeks), not acceptable. CEVA recommendations without defined protocol or precise data. No more "checkable" guarantees on auto-vaccines, strains may vary from one year to the next</p> <p>Quinolone use possible but too late (post AB gram) => 25 to 50% mortality - multi-resistance (average: 16% in meat sheep, 10% in milk sheep)</p>		A	<p>Existence of the IMOCOLIBOV vaccine, with marketing authorisation for sheep. Vaccine usable in goats but with fixed WP, which will be 1 day with NVR.</p> <p>Auto-vaccines (but development too long). Overall, strengthening sanitary and zootechnical measures (colostral intake) seems an interesting solution.</p>		n°2	
Sheep scabies	<p>Too many macrocyclic lactone treatments, consequent resistance risks on digestive strongyles. New serological tool ID.</p>		A	<p>Balneations but difficulties in the elimination of treatment products & user safety concerns.</p>		n°3	

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Myiasis due to <i>Wohlfahrtia magnifica</i> and <i>Lucilia sericata</i>	Geographical extension of myiasis due to <i>Wohlfahrtia</i>. Lack of effective treatments because of the specific location of these myiasis and their seasonality (insufficient duration of action of existing drugs). Lack of efficacy of the CLIK pour-on on areas without wool and under the hoof (manual removal required). Record of 16 PhV declarations (lack of efficacy), of which only 3 since 2015: how this problem evolves?		A	Use of essential oils (need to inform users on risks), BUTOX or VERSATRINE (off-label).		n°4	
Border disease	No efficacy of the vaccine for cattle. No foetal protection.		C	Bovine vaccine only but not effective		n°5	
Respiratory pasteurellosis (with increased prevalence of <i>Pasteurella multocida</i>)	OVILIS PASTOVAX moderately effective in sheep (because of the low number of strains in the vaccine), operates moderately in goats. PhV statements (lack of efficacy): 26 in sheep, 11 in goats. Critical lack of a <i>Pasteurella</i> vaccine for goats (+ atmosphere parameters to be adjusted). The typing of <i>Pasteurella</i> strains cannot be done currently: it is an issue. Auto-vaccine, yes but: - Sampling matrix (deep nasal swab, lung, etc.) not allowed if non-genotyped resistant animal to EST. Difficult in goats unlike sheep - Pharmacovigilance showing the lack of efficacy of a commercial vaccine adapted to the isolated strain - Absence of the <i>Mannheimia haemolytica</i> serotype from the commercial vaccine (but serotyping problem, etc.).		A	Mixed vaccine combining useless <i>Salmonella</i> strains (SALMOPAST) or specific vaccine but not including all strains involved in ovine and caprine disease (OVILIS PASTOVAX). Auto-vaccines (see opposite)			n°2
<i>Mycoplasma mastitis</i>	Two intramammary antibiotics "for dry period" with MA for sheep, and only 1 for goats (NAFPENZAL): are not effective on <i>Mycoplasma</i> (resurgence in certain regions). No available vaccine solution: cascade use not even possible. No vaccine. Auto-vaccine efficacy? Critical in goats => culling	X	A	Possibility of importing live vaccines from Spain (<i>M. agalactiae</i>) AGALAX Tres, AGALAX Uno but of risky use (inactivated vaccine). Autovaccine If lack of efficacy is declared: production of an auto-vaccine is possible from isolation in milk.			n°3
Paratuberculosis	Absence of vaccine in France		C	Possible import of the Spanish GUDAIR vaccine (many import requests) and less expensive than Silirum.			n°4

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Contagious ecthyma (scabby mouth, orf virus)	Mortality of lambs and mammals (viral disease). A commercial vaccine exists (ECHTYBEL®) with variable results (better efficacy via intradermal than subcutaneous route) – effective in 70% of cases in sheep when used in ID and curative (as soon as the first lesions appear). No PhV declarations. ECHTYBEL availability concerns - to be monitored (ANMV).		C	Possible OVERVAC® import. Last import was in 2017 (suspected pestivirus strains contamination in the imported vaccine). Various alternative therapies (homeopathy, phytotherapy, etc.) Echtymatisation (scarification from samples of crusts taken from infected herd): isotherapy prohibited.			
Prevention of staphylococcal dermatosis of teats / mastitis	Unknown efficacy of VIMCO. Not conclusive on cell counts. No indication for staphylococcal dermatosis. Difficult to conclude on efficiency (due to the impact of the Morel Micrococcus). <i>A priori</i> not effective on goats. No efficacy information on sheep. The farmers who vaccinate are those with the best milking techniques. Few reports of lack of efficacy (2 in sheep and 2 in goats). Many farms use amoxicillin or penicillin.	X		VIMCO® (Hipra) indicated for staphylococcal mastitis for sheep and goats with the following claim : Reduction of subclinical mastitis			
Anti-inflammatory drugs, analgesics	No NSAIDs with MA for sheep: Animal welfare issues for convenience operations (i.e caudectomy, dehorning, etc.). Absence of defined milk withdrawal period. => Absence of pain control in dairy sheep and goats	X	C	No drugs with MA for sheep. => drugs authorised for cattle with following withdrawal periods (WP): Flunixin meglumine: 24 to 36h for milk, 10 to 31 days (IM) for meat & offals Dexamethasone: 11 MA (in France) for goats with milk WP of 3 to 7 days, no MA for sheep			
Q fever	COXEVAC: no MA for sheep		C	COXEVAC, vaccine (MA 2010) "phase 1", but indicated only in cattle and goats and without MA in sheep			
Caseous disease or caseous lymphadenitis	Absence of vaccine in France Use of auto-vaccines (risk???) is possible in the theoretical case of a lack of efficacy of the imported vaccine. However, the efficacy of auto-vaccines is low (low immunogenic agent). Less critical disease in sheep, more in goats.		A	Possible import of a Spanish vaccine for caseous lymphadenitis with <i>Corynebacterium pseudotuberculosis</i> (rare in sheep). Abscess disease due to the Morel micrococcus (staphylococcus) can be prevented using VIMCO® (Hipra) with cross-protection (<i>Staphylococcus aureus</i> / Morel micrococcus); efficacy questioned.			
Piroplasmosis	No VMP with MA in sheep. The CARBESIA meat WP of 213 days is not applicable.		A	Single VMP with MA for cattle: CARBESIA			
Uterine infections	No VMP with MA – only VMP authorised in the bovine species		A	HISTABIOSONE: MA for goats. Compliance with the fixed WP of the cascade is not problematic in this case.			
Ringworm	Absence of vaccine with MA for sheep and goats		C	Vaccine authorised in cattle (Bovilis RINGVAC). IMAVERAL but no MA for sheep or goats			

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Hormones	<p>WP issues for CHRONOGEST LC goat sponges: 36 h whereas 0j for SYNCROPART and CHRONOGEST CR.</p> <p>Efficacy concerns in sheep (young prepubescent animals) - see livestock management.</p> <p>Ethical problem of PMSG production (on pregnant mares). Impact ++ (in non-organic sector) in case of unavailability</p>		A	Flugestone sponges in goats			
ONS (sheep) Nasal obstruction syndrome	<p>Disease in a regional context (Basque Country), with imprecise aetiology, but involving <i>Oestrus ovis</i> infestations associated with local hypersensitivity reactions.</p> <p>The control of oestrosis in milk sheep farming remains problematic due to the WP of active molecules against the parasite.</p>		C				
Taeniasis	<p>CESTOCUR: too concentrated (3 mL/20 kg) to be used on young animals. Lack of efficacy because volume is too low.</p> <p>Report of 9 declarations of lack of efficacy in sheep between 2015 and 2020.</p>		A				
Intramammary	<p>Only 2 intramammary VMP available in sheep (NAFPENZAL T and CEFOVET HL) and only 1 in goats (NAFPENZAL T).</p>	X					
Adenomatosis (sheep)	<p>Big problem affecting "Causse lambs" production (affecting adults)</p>		A	None	X		
Visna maedi (sheep)(lentivirus viral disease)			A	Slaughter of the herd	X		
Footrot	<p>No licensed vaccine for lactating ewes</p>	X			X		

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Resolution in progress	EXISTING solution						
Treatments for flies	There are no VMP against flies with short milk WP (fixed WP is 7 days in case of "cascade use" of VMPs not authorised in the species)	X	C	VMP with MA for sheep & goats: SEBACIL, EPRINEX multi (milk WP=0j), DIMPYGAL (milk WP=4 milkings). With NVR, the "cascade fixed WP" will be 1.5x that for cattle or 1day if 0 day. => milk WP in sheep and goats will be of 1 day for FLECTRON and DELTANIL pour-on and 1.5 day for BUTOX and VERSATRINE			
Antispasmodic (sheep, goats)	No genital antispasmodic for females. Difficulties of intervention on non-dilatations of the cervix, spills of vagina or uterus. Ether, alcohol swab		A	SPASMIPUR: MA for sheep with milk WP of 12 h PLANIPART with MA only for cattle CERVICYL (homeopathic medicine) but inconsistent efficacy.			
Urolithiasis (phospho-ammoniac magnesium stones) (rams)	Discontinuation of antispasmodic: phloroglucinol (SPASMOGLUCINOL ND) No more access to ammonium chloride		A	Only alternative: surgical SPASMIPUR?			
Schmallenberg disease	No vaccine available. ZULVAC SBV. Vaccine not used because of natural immunisation.		A	Solution now existing.			
Salmonella abortions	Reminder: Discontinuation of marketing for several years of a attenuated vaccine (SALMOVIS) with satisfactory efficacy. Salmonella diarizonae: Emergence over the last 4 years in various regions (central west, south-east, Normandy). Abortions, contamination of raw milk. Zoonotic disease. Absence of systematic detection if not requested.		A	Salmonella abortus ovis: New INMEVA vaccine (MA 04/2019): satisfactory feedback. Last request in 06/2019 for the bivalent vaccine (<i>Salmonella abortus ovis</i> , <i>Chlamydia abortus</i>): OVIVAC CS (Hipra). Salmonella diarizonae: Auto-vaccine : very long to obtain (10 wk for Filavie on 1st request). Sampling matrix: foetal annexes (genotyping required) or milk. Hygienic measures			
Fasciolose	Triclabendazole is the only active molecule on young immature of <i>Fasciola hepatica</i> .		C/A	TRIBEX 5%: MA specific for sheep			
Anaesthetics		X		WP for milk, meat and offals of 0 days for Xylazine (ROMPUN® etc.) and Ketamine (KETAMIDOR®). 3 VMPs with Ketamine and MA for sheep and goats (ANAESTAMINE, IMALGENE, KETABEL) with milk WP of 0 day Procaine (PROCAMIDOR®): MA for sheep with milk, meat & offals WP of 0 day			