

## Therapeutic gaps in the RABBITS sector

### Meeting of 13/06/22

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Pathology	<b>Problem encountered:</b> <b>PhV:</b> Pharmacovigilance (unsatisfactory efficacy or safety) <b>Disp:</b> Availability, disruption <b>Rule:</b> Regulatory (cascade application, waiting time, restricted access) <b>0 MV:</b> No veterinary drugs for species/indication <b>0 ST:</b> No therapeutic solution	<b>Problem type:</b> PhV Disp Rule 0 MV 0 ST	<b>Alternatives identified (post-meeting additions)</b>	<b>PRIORITIES</b> Major: <b>M</b> minor: <b>m</b> (Health / economic impacts)
<b>Respiratory disorders due to pasteurelles, mycoplasma and/or bordetella</b>	<ul style="list-style-type: none"> <li><b>No vaccines available with marketing authorisation for rabbits.</b> Vaccines for ineffective pigs or poultry on rabbits.</li> <li><b>Antibiotics (ATB) still widely used</b>                              ⇒ <b>serious health and economic impact</b> (particularly among young people).                              ⇒ <b>Risks of multiresistant staphylococcus augmentation</b> with the increasing use of macrolides (effective on pasteurelles).</li> <li><b>Problem of waiting time (BP) cascade of 63 days (=1.5x calf BP) for oral tilimicosin:</b> not applicable for rabbits slaughtered at 70 days, whereas Elanco studies would allow a BP of 4 days (=BP tilimicosin premix with rabbit MA) for rabbits?</li> <li><b>Oxytetracyclines ± effective</b> (TA should be defined by manufacturers for rabbit).</li> <li><b>Autovaccines containing only Pasteurella valencia of limited efficacy.</b> Good efficacy of staphylococcus or mycoplasma autovaccines. INRA work on the possibility of obtaining genetic resistance to pasteurelles has not led to practical consequences. Demonstrated link between mycoplasmosis and respiratory disease</li> </ul>	<b>0 MV</b>  <b>Rule</b>  <b>PhV</b>	<ul style="list-style-type: none"> <li>➤ <b>Widely used antibiotics (ATB)</b> (macrolides, tetracyclines, sulfonamides-trimethoprim), particularly in maternity and fattening in drinking water. <u>ANMV sales review/monitoring:</u> according to the declarations of the MA holders, between 2019 and 2020 there was an increase in exposure to Macrolides in the form of premixes, observation not confirmed by the monitoring of drug food uses. Tetracyclines use decreased and Sulfamides-TMP use increased in 2019 and 2020 vs 2018.</li> <li>➤ <b>Self-vaccines</b> (no request recorded at the ANMV). <b>Highly virulent staphylococci have almost disappeared and the lack of efficacy of autovaccines against pasteurelles does not encourage the practitioner to prescribe them.</b></li> <li>➤ <b>Breeding techniques</b> (ventilation).</li> <li>➤ <b>Phyto products</b> (via food, inhalation or drinking water): “excellent results” by inhalation or drinking water if a phytogram validates in the lab their effectiveness on the bacterial strain concerned. Quote by one of the participants of a product whose</li> </ul>	<b>M</b> <b>#1</b>

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	<p>➤ <b>Consider developing a bivalent rabbit vaccine?</b> Presence of mycoplasmas rarely revealed as there is a problem of technical difficulty in isolation. However, in 1994 it was shown that mycoplasma is very common in cuniculture Bordetelles = "superinfectant". Lack of studies to specify their role: pathogenic, permissive, co-pathogenic?</p>		composition they do not know is used in scheduled distribution (a few minutes).	
<b>Coccidiosis</b>	<ul style="list-style-type: none"> <li>• <b>Residue problem when applying existing TAs of 8 or 12 days</b> (see multiple publications). Following the detection of exceeding MRLs during exports (Japan in particular), the sector voluntarily applies a 21-day BP to drugs containing sulfadimethoxin =&gt; poor image of the final product and risks for export. No residue problem <b>if used in drinking water with a BP of 21 days, but problem of solubility at non-neutral pH</b> of the TMP/Sulfamides combinations. <ul style="list-style-type: none"> <li>➤ <b>Veterinarians expect additional studies of these marketing authorisations to be taken into account by manufacturers for greater safety in the prescription.</b></li> </ul> </li> <li>• <b>Limited efficacy of additives such as robenin (many resistances)</b></li> <li>• <b>Development of ground breeding (for animal welfare - BEA) which encourages</b> the increase in parasitosis including coccidiosis and <b>the risk of resistance (AMR)</b> if only authorised drugs for rabbits are used systematically <ul style="list-style-type: none"> <li>➤ <b>Interest in marketing authorisations for rabbits for other anticoccidians</b></li> </ul> </li> </ul>	<p><b>PhV</b></p> <p><b>PhV</b></p>	<p>➤ <b>ATB (sulphonamides - see opposite)</b> For information: solubility tests planned for the ANMV in 2022 for certain antibiotic drugs.</p> <p>➤ <b>Anticoccidians:</b> Additives (decquinat) allowed in the food but used for 28 days too long to be economically interesting. Cascading use of veterinary drugs (PV) with marketing authorisation for other species now possible thanks to the new 2019/6 regulation (NVR) which allows more favourable flat-rate TAs: Diclazuril: flat-rate TAs of 1 day with drinkable PV. MRLs for rabbits were published in 2014. Toltrazuril oral: BP 14 days for poultry and 61 to 77 days for pigs =&gt; fixed long BP in rabbit breeding (even if MRL for all mammalian species published in 2005). Bayer studies showed a reasonable BP of 35 days. It would be interesting to be able to formalise this data.</p>	<b>M no. 2</b>
<b>Moth</b>	<ul style="list-style-type: none"> <li>• <b>No drug with MA rabbits.</b> Even though cases are infrequent in livestock farming and have little impact on weight gain, this can be problematic because it involves <b>zoonosis with contamination risks</b> for farmers, employees, visitors, neighbours and families. To date, eradication in multipliers.</li> <li>• Moth does not cause mortality in breeding and, apart from extreme cases of zoonosis, farmers do not want to spend a</li> </ul>	<p><b>Disp</b></p> <p><b>Rule</b></p>	<p>➤ <b>Imported foreign vaccine (BIOVETA) for <i>Trichophyton mentagrophytes</i>:</b> a recent request to the ANMV for approximately 7,500 doses (= all of France). Nothing for moth due to <i>Microsporium canis</i>.</p> <p>➤ <b>Cascade use of IMAVERAL:</b> marketing authorisation only for cattle and equines with a BP = 0 days – no MRL required for topical use in these species. <b>1d cascade TA for rabbits.</b> In general, 2 sprays are carried out 4 days apart.</p>	<b>M No. 3</b>

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	lot of money on treatments for minimal results (no scientifically established moth protocols in breeding).			
<b>Ear drops</b>	<ul style="list-style-type: none"> <li>• <b>No medicinal product with MA flesh rabbits.</b></li> <li>• Disappearance of acaricides usable in the environment.</li> </ul> Uncommon disease in modern farms, encountered mainly in farms with porous materials (wood, stone) and in farm farms.	<b>Rule</b>	➤ <b>Cascade use of avermectins:</b> injection on adults and breeders (flat-rate BP is not a problem) A residue depletion study would nevertheless be interesting.	<b>m</b>

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Resolution in progress	Existing solution	Reason for resolution in progress / disappearance of the therapeutic gap		
<b>Clostridium perfringens or Clostridium spiroforme funotoxemia</b>	<ul style="list-style-type: none"> <li>➤ Bacteria that contribute to digestive instability: oral antibiotics are widely used for Clostridies/EEL+/-Coccidies syndrome, <b>impact on risks of antibiotic resistance (AMR).</b></li> <li>➤ <b>No vaccines containing C. spiroform</b></li> </ul>	<b>Rule</b>	<ul style="list-style-type: none"> <li>➤ <b>ATB (primarily tiamulin and bacitracin)</b> ANMV sales review/monitoring: increase in exposure to bacitracin since 2019 (also increase for 2021 as increase in volumes sold vs 2020). Decrease in the use of Pleuromutilines since 2017.</li> <li>➤ <b>Rabbit vaccines available:</b> COGLAVAX and COGLAMUNE containing <i>Clostridium perfringens</i> type A, C and D <b>but not C. spiroform.</b></li> <li>➤ <b>Breeding techniques (rationing, ventilation)</b> generally make it possible to reduce the incidence</li> </ul>	<b>M =&gt; m</b>
<b>Oxides</b>	<ul style="list-style-type: none"> <li>• <b>No MA rabbits</b> for effective pest control agents (benzimidazoles). <b>Only flubendazole kills all stages</b> (including eggs and larvae) of this parasite which develops in the cecum of rabbits. Allows treatment (the rabbit oxide cycle is about fifty days) every 84 days. Fenbendazole, oxfendazole for example, does not kill eggs or small larvae and therefore requires several treatments 42 days apart. Levamisole widely used in the past is no longer effective.</li> </ul>	<b>Rule</b>	<ul style="list-style-type: none"> <li>➤ <b>Possible cascade use of drinkable MV available</b> with more favourable flat-rate TA <b>since NVR:</b> Flubendazole oral: FLIMABO and FLIMABEND - TA meat &amp; offal Pork = 3 or 4 days depending on poso, Chickens = 2 days; <b>=&gt; flat-rate TA for rabbits ≥ 6 days</b> PANACUR Aquasol 200 mg/mL - TA meat &amp; offal Pork = 4 days, Chickens = 6 or 9 days depending on poso <b>=&gt; Fixed BP for rabbits ≥ 6 days</b> <b>Female de-parasite before weaning</b></li> </ul>	<b>m</b>
<b>Follicular stimulation (follicular maturation)</b>	<ul style="list-style-type: none"> <li>• <b>AMM requirement on specific PMSG.</b> HR management is carried out on the day of the AI and cannot replace the PMSG carried out a few dozen hours before. But fewer and fewer farmers use it except on primipares.</li> </ul>	<b>Rule</b>	<ul style="list-style-type: none"> <li>➤ <b>Breeding techniques:</b> overlapping with another rabbit is enough to stimulate follicular maturation.</li> <li>➤ Prostaglandins (off-label but not very troublesome)</li> </ul>	<b>m</b>
<b>LV staphylococci</b>	<ul style="list-style-type: none"> <li>• Yet another case of prododermatitis. Various strains, some close to <i>S. community human aureus</i> (publications on this point).</li> </ul>	<b>PhV</b>	<ul style="list-style-type: none"> <li>➤ <b>Breeding techniques:</b> foot rest on duckboards</li> <li>➤ <b>ATB: systemic antibiogram.</b> In general, use of macrolides, tetracyclines and sulfonamides-TMP.</li> <li>➤ Self-vaccine (partial solution): no requests to the ANMV to date.</li> </ul>	<b>m</b>

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<p><b>Colibacillose to E. O103 PCR <i>eae</i> positive or with lesions</b></p>	<p>Less common condition (stopping farms).</p>	<p>PhV</p>	<ul style="list-style-type: none"> <li>➤ <b>Breeding techniques:</b> sanitary void</li> <li>➤ Oral vaccine against colibacillose at O103 Rh (no commercial name to date) works very well if administered on a case-by-case basis (INRA e trials) and very difficult to administer to a group of animals. But it is not marketed)</li> <li>➤ ATB: fluoroquinolones, colistin, neomycin, spectinomycin, gentamycin, apramycin drinking water</li> </ul>	<p>m</p>
<p><b>VHD new variant</b></p>	<p><b>ANMV meeting with the sector on 19/03/20:</b> New variant HDV vaccines: insufficient efficacy, challenged CPR protocols and too high cost for mass fattening vaccination. Very tense situation with 28% of farms affected in 2018 and 26% in 2019 despite the control plan put in place. <b>10% of HDV-related terminations in 2018 and 35% in 2019.</b></p>	<p>PhV</p>	<ul style="list-style-type: none"> <li>➤ <b>ATU vaccines</b> (ATU for Filavac VHD VAR K renewed in Nov 2021) were very useful in controlling the situation. A single injection is usually sufficient.</li> <li>➤ <b>Financial support (FMSE fund) for vaccination of fattening batches.</b></li> <li>➤ <b>Good training for farmers</b> to detect 1st signs.</li> <li>➤ <b>Essential epidemiological monitoring, to be maintained. As well as biosecurity measures.</b></li> <li>➤ <b>2 new vaccines</b> have been available since 2019:             <ul style="list-style-type: none"> <li>- FATROVAX RHD KC+V 1 (Fatro) - AMM 16/08/21</li> <li>- NOBIVAC MYXO-RHD plus (MSD) – AMM 19/11/19</li> </ul> </li> </ul>	
<p><b>Inflammation and pain</b></p>	<ul style="list-style-type: none"> <li>• <b>No medicinal product with MA flesh rabbits.</b></li> </ul> <p>Lack of data on the interest of an antiinflammatory agent in combination with antibiotic treatment and treatment protocol. Off-label use of paracetamol and meloxicam.</p>	<p>Rule</p>	<ul style="list-style-type: none"> <li>➤ <b>Cascade use of veterinary drugs (VM) with marketing authorisation for other species</b> now possible with a more favourable flat-rate TA thanks to the new regulation 2019/6 (NVR): Paracetamol has an MRL status only for pigs orally (meat TA=0d) =&gt; cascade use possible for rabbits with flat-rate TA of 1d Meloxicam has an MRL status in rabbits =&gt; it is not the MRL status that blocks the development of a marketing authorisation. METACAM 15mg/mL Oral suspension – meat TA = 3d for horses, 5d for pigs =&gt; <b>cascade use possible for rabbits with flat-rate TA of 8d.</b></li> </ul>	<p>m</p>
<p><b>HV staphylococci</b></p>	<p><b>There are now no more cases.</b></p>	<p>PhV</p>	<p>ATB, self-vaccine Self-vaccine (partial solution, no eradication): no request to the ANMV to date.</p>	<p>m</p>

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Actions	Who	Due date
<b>Respiratory disorders</b>		
➤ Communication on the interest of mycoplasma and pasteurella bivalent vaccine for rabbits	RFSA (via meeting minutes)	15/07/22
➤ Communication on the interest of a marketing authorisation for rabbits (respiratory disorders) for tilmicosin oral solution (marketing authorisation for other species for MV Elanco, Dopharma, Huvepharma, Lavet), with depletion data authorising a TA applicable to poultry farming (4d? as for premixes with AMM rabbits, instead of 63j=1.5 x calf BP)	RFSA (via meeting minutes)	15/07/22
➤ Data on uses of plant protection products in cunicole farms (during respiratory disorders)?	Sector?	???
➤ Solubility control of certain antibiotics for drinking water	ANMV	12/2022
<b>Coccidiosis</b>		
➤ Information on use cascade possible for diclazuril oral and on the interest of a rabbit AMM extension with any reductions (Art 23) and protection period (Art 40.5)	RFSA (via meeting minutes)	15/07/22
➤ Search for residue data available when used in the oral toltazuril rabbit to find out if an MA extension would be interesting (cascade use now requires BP ≥ 1.5x14 or 77j – to be confirmed)	ANMV via Elanco	
<b>Moth</b>		
➤ Make BIOVETA aware of the importance of maintaining the availability of their moth vaccine ( <i>Trichophyton</i> ) and desire for an MR for France	RFSA (via meeting minutes) ANMV	15/07/22
<b>Ear drops</b>		
➤ What residue depletion data are available when injecting rabbits?	ANMV	12/2022