

Therapeutic gaps in the RABBITS sector

Hearing on 30/04/24

Participants: Samuel BOUCHER (representative of the SNGTV Rabbit Commission, veterinary practitioner in Vendée); Olivier SALANDRE (representative of CSMV, veterinarian General manager of Chêne Vert Conseil in Châteaubourg,); Claire CHAUVIN (veterinarian, Anses Ploufragan)

Excused: Sophie LÉBOUQUIN-LENEVEU (veterinarian epidemiologist, Anses Ploufragan)

for ANMV: Laure Baduel; Béatrice Leroux; Caroline Guittre; Anne Sagnier; Sandrine Rougier; Laurent Fabry

Reminder of the responsibility for the comments expressed during the hearing and reported in this report:

- The identification of therapeutic gaps (and details of the situations expressed and the alternatives envisaged) is the responsibility of the representatives of the veterinary profession
- The ANMV provides additional information or answers to the technical-regulatory questions addressed. These supplements are systematically preceded by “ANMV Info: ...”, to distinguish the origin of the words expressed.

Conclusion and evolution of gaps since the last hearing in June 2022: see p9

Table summarising the comments of representatives of the veterinary profession (new elements since the last hearing – in blue):

Disease	Problem encountered: PhV: Pharmacovigilance (efficacy or safety perceived as unsatisfactory) Disp: Availability, shortage Reg: Regulatory (cascade application, withdrawal period, restricted access) 0 VMP: Absence of appropriate veterinary medicinal products (VMPs) 0 TS: Lack of therapeutic solution	Problem Type: PhV, Disp, Reg 0 VMP 0 TS	Alternatives identified	PRIORITY Major: M minor: m (see p8)
Respiratory disorders due to pasteurella, mycoplasma and/or bordetella	<ul style="list-style-type: none">• Still no vaccines available with MA for rabbits. Vaccines for pigs or poultry ineffective on rabbits. <i>Pasteurellosis associated with mycoplasma in respiratory forms, is one of the most common diseases with almost 100% carriers</i>• Antibiotics (ATBs) still used ⇒ health and economic impact ⇒ Risks of increased multiresistant staphylococci with the use of macrolides (effective on pasteurella).• <i>Almost no more plants manufacturing medicated feed</i>• Problem of cascade withdrawal period (WP) of 63 days (=1.5x WP for calves) for oral tilmicosin: not applicable for rabbits	0 VMP Reg	➤ Antibiotics (ATB) : oral use (macrolides, tetracyclines, sulfonamides-trimethoprim), particularly in maternity and fattening units. <i>ANMV info on antibiotic sales assessment/monitoring: Evolution of exposure between 2017 and 2022: -78% for macrolides (-91% between 2021 and 2022) -34% for tetracyclines -30% approximately for sulfonamides-trimethoprim</i>	M n°1

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	<p>slaughtered at 70 days, whereas Elanco studies would allow a WP of 4 days (=WP of tilmicosin premix with MA for rabbit) for rabbits ?</p> <ul style="list-style-type: none"> • Oxytetracyclines ± effective (WP should be defined for rabbits by MA holders). ANMV Note: WP is 7 days for powders for oral solution and 14 days for medicated premixes. • Autogenous vaccines containing only Pasteurella strains have limited efficacy. Good efficacy of autovaccines against Staphylococci or Mycoplasma. Demonstrated link between mycoplasmosis and respiratory disease ➤ Consider the development of a bivalent vaccine for rabbits? Presence of mycoplasmas rarely revealed because of technical difficulty in isolation. However, in 1994 it was shown that mycoplasma is very common in rabbit farming. Bordetella = "overinfecting". Lack of studies to specify their role: pathogenic, permissive, co-pathogenicity? The INRAe RELAPA work on the possibility of obtaining genetic resistance to pasteurella didn't translate into practical consequences. ANMV Info: No new MAs since the previous hearing (13/06/2022). Anses Info: Résapath data show an increase in resistance of pasteurella to quinolones. S.Boucher's comments: enrofloxacin, which has an MA, is practically no longer used in farms but is widely used by vets for companion rabbits. Oxolinic acid is not used in the rabbits sector. Sometimes other quinolones such as flumequine can be used. Please clarify what resistance is referred to, as antibiograms include non-prescribed substances (e.g. nalidixic acid) to monitor the risk of bacterial resistance to the latest generation of quinolones. 	<p>PhV</p>	<p>There are no longer declared sales of tilmicosin premixes in 2023. There are still 5 oral solutions sold, but without MA for rabbits (TILMOPRO, PULMOVET, PULMOTIL AC, TILDOSIN and TILMOVET) Sales of medicated feed: tonnage decreased by 65% between 2021 and 2022.</p> <ul style="list-style-type: none"> ➤ Autogenous vaccines Highly virulent staphylococci have almost disappeared and the lack of efficacy of autovaccines against pasteurella does not encourage the practitioner to prescribe them. ➤ Breeding techniques (ventilation). ➤ Plant based products (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. Frequent use, variable depending on the customer and the prescriber, not always trained. Finished products based on mixtures of plants and essential oils are formulated by specialised veterinarians (with University Diploma). They're manufactured in factories. These products are then tested in laboratory before prescription, using phytograms, same as antibiograms are carried out before antibiotic prescription. Very positive feedback. This is a reasoned and pragmatic use, even if these are products without MA, knowing that MA would be desirable. All substances in the products formulated by the specialised vets have an MRL status. ANMV Info: strong involvement of ANMV at European level in the recognition and facilitation of the use and approval of herbal medicines. Ongoing development of a methodology for submitting MRL files. 	
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<p>Coccidiosis</p>	<ul style="list-style-type: none"> • Residue problem when applying existing WPs of 8 or 12 days (see multiple publications). Following the detection of residues exceeding MRLs in case of exports (to Japan in particular), the sector nowadays voluntarily applies a 21 days WP for VMPs containing sulfadimethoxin => poor image of the final product and risks for export with refusal from certain slaughterhouses, from certain countries (e.g. Switzerland) and restrictions in the specifications. ANMV Info: We have received only one declaration in 2008 reporting a residue problem beyond 8 days of WP after TMP-sulfa treatment. Nothing since then. S.Boucher’s comments: Unfortunately, pharmacovigilance cases are poorly reported, and even more at that time. Official controls reported these cases in the sector. There were several per year. This is what led us to conduct expensive studies. <p>No residue problem if used in drinking water with a WP of 21 days, but solubility problem of the TMP/Sulfonamides combinations occurred at a non-neutral pH.</p> <ul style="list-style-type: none"> ➤ Veterinarians expect additional studies to be taken into account by manufacturers for more safety in the prescription. <p>ANMV Info: creation of a new appendix (FR: rapporteur) in the guideline on the quality of VMPs to be administered through drinking water where contact with biocides must be tested to check the compatibility/stability of the VMP. This appendix will apply from 1 October 2024 for pharmaceutical companies see https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L_202401159 Recent publication of the Regulation “Oral administration of veterinary medicinal products”</p> <ul style="list-style-type: none"> • Limited efficacy of additives such as robenidin (many resistances) • Development of ground breeding (for animal welfare consideration) which encourages the increase in parasitism 	<p>PhV</p> <p>(1) VMP</p>	<ul style="list-style-type: none"> ➤ ATB (sulfonamides – solubility problem - see opposite) For information: solubility controls have been carried out. ANMV post-meeting info: following these controls, recommendations were introduced if necessary by the MAHs in the SPCs of the concerned VMPs. ➤ Anticoccidials: Additives (decoquinate) allowed in the food but use for 28 days is too long to be economically attractive. In addition, food factories no longer want to incorporate them. <p>The “cascade use” of VMPs with MA for other species is now possible thanks to Reg 2019/6, which allows more favorable WPs:</p> <ul style="list-style-type: none"> - Diclazuril: WP of 1day with VMPs for oral use. MRLs for rabbits were published in 2014. Widely used in drinking water and premix - Oral toltrazuril: WP of 14 days for poultry and 61 to 77 days for pigs => long WP should be applied for rabbits (even if MRLs for all mammalian species were published in 2005). Bayer studies would have shown that a shorter WP of 35 days would be sufficient => possible use only on mothers. It would be interesting to be able to formalise those data. ANMV Note: If they are not too old data to meet current standards... - Amprolium: off-label use (MA only for poultry), with satisfactory results. However, a few years ago, cases of suspected intoxication were suspected in France, prompting some insurance companies to ask the vets concerned to stop such prescription. These data are very old (over 30 years) but are currently holding back prescribers. => Wish for conducting and participating in a well-defined trial to specify safety (and efficacy) data in growing rabbits. Is there any literature on the subject, knowing that it is used in North Africa and in pet rabbits in the UK ? Post-meeting ANMV info: existing MRL status for poultry (Annex II) for oral use only, and without mention of 	<p>M n°2</p>
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	<p>including coccidiosis and the risk of resistance (AMR) if only authorised VMPs for rabbits are systematically used.</p> <p>➤ Interest in MAs for rabbits for other anticoccidials</p>		<p>restrictions on use in rabbits see EPMAR: amprolium-summary-report-2-committee-veterinary-medicinal-products_en.pdf (europa.eu).</p> <p>Since the WP is zero days in poultry, the “cascade” WP will be one day for rabbits, as they belong to a different taxonomic family – see Art 115 of Reg 2019/6.</p>	
Ringworm	<ul style="list-style-type: none"> • No VMP with a MA for rabbits. Even though cases are infrequent in livestock farming and have little impact on weight gain, this can be problematic because it is a zoonosis with risks of contamination for breeders, employees, visitors, neighbours and families. Slaughterhouses are starting to refuse contaminated animals. To date, eradication in multipliers. • Ringworm does not cause mortality in farms and, apart from extreme cases of zoonosis, farmers do not want to spend a lot of money on treatments for minimal results (no scientifically established protocols against ringworms in farms). • Itraconazole: too expensive in rabbit breeding and inappropriate use (7 days of treatment, 3 times at one week apart) • Big problem because of slaughterhouse refusal as soon as there are lesions. 	0 VMP	<ul style="list-style-type: none"> ➤ Imported vaccine (BIOVETA) for <i>Trichophyton mentagrophytes</i>: Bioveta has stopped distribution. Post-meeting ANMV info: 2 vaccines against ringworm are authorised in Bulgaria with MA for Rabbits (VERMET with <i>T.verrucosum</i> and <i>T.mentagrophytes</i> and ПОЛИДЕРМ with <i>T.mentagrophytes</i> and <i>Microsporum canis</i>) ➤ Nothing for ringworm due to <i>Microsporum canis</i> (rarer). Post-meeting ANMV info: see above ➤ Cascade use of IMAVERAL: MA only for cattle and horses with a WP of 0 day – no MRLs required for topical use in these species => 1 day “cascade WP” for rabbits. In general, 4 sprays are performed 4 days apart. But not effective: need for a more important application on the skin. 	M n° 3
Ear scabies	<ul style="list-style-type: none"> • No VMPs with MA for rabbits. • Disappearance of acaricides that can be used in the environment. <p>Uncommon disease in modern and “clean” farms, encountered especially in farms with porous materials (wood, stone) and in traditional farm breeding. Its incidence has decreased significantly.</p>	Reg	<ul style="list-style-type: none"> ➤ Cascade use of avermectins: injection on adults and breeders (for which cascade WP is not a problem) A residue depletion study would nevertheless be interesting. ANMV Info: 1 article with doramectin (Shen et al, 2009 see https://doi.org/10.4315/0362-028X-72.10.2189). The WP would be 23 days. 	m

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Resolution in progress	Existing solution		Reason for ongoing resolution / disappearance of the therapeutic gap
<p>Enterotoxaemia due to <i>Clostridium perfringens</i> or <i>Clostridium spiroforme</i></p>	<ul style="list-style-type: none"> ➤ Bacteria that contribute to digestive instability: oral antibiotics are widely used for Clostridium/EEL+/-Coccidial syndrom, impact on risks of antimicrobials resistance (AMR). ➤ No vaccines containing <i>C.spiroforme</i> 	<p>Reg</p>	<ul style="list-style-type: none"> ➤ ATB (mainly tiamulin and bacitracin) Sales ANMV assessment/monitoring: In 2022, we returned to the same level of bacitracin exposure as in 2017. Strong decline in exposure to Pleuromutilin, which continues: -64% between 2017 and 2022. Significant declines were recorded in 2022 compared to 2021, notably for Pleuromutilin (-54.3%). These decreases in one year are mainly due to the important decrease in the use of medicated feed. There does not appear to be any transfer of exposure to powders and oral solutions. Note: new MA (23/06/23): KARIMULINA 101.2 mg/ml solution for administration in drinking water for rabbits. This oral solution is added to the 2 others already marketed (Vetmulin and Cevamuline) and the Tiamuval Premix which is also still marketed. ➤ Vaccines available for rabbits: COGLAVAX (COGLAMUNE no more marketed) containing <i>Clostridium perfringens</i> type A, C and D but not <i>C.spiroform</i>. Very little used, too expensive in growing rabbits. ➤ Husbandry techniques (rationing, ventilation) are generally effective in reducing the incidence
<p>Follicular stimulation (follicular maturation)</p>	<ul style="list-style-type: none"> • MA wished for specific PMSG (only for 15 to 20% of farms). GnRH is performed on the day of the AI and cannot replace the PMSG given a few dozen hours before. But fewer and fewer farmers use it, except on primiparae. 	<p>Reg</p>	<ul style="list-style-type: none"> ➤ Breeding techniques: riding by another queen is enough to stimulate follicular maturation. ➤ Prostaglandins (off-label but not very problematic)
<p>Colibacillosis due to <i>E.coli</i> O103 PCR <i>eae</i> positive or with lesions</p>	<p>Less frequent condition (cessation of livestock farming).</p>	<p>PhV</p>	<ul style="list-style-type: none"> ➤ Breeding techniques: sanitary void ➤ Oral vaccine (without commercial name to date) against colibacillosis due to O103 Rh works very well if administered on a case-by-case basis (INRAe trials) and very difficult to administer to a group of animals. But it is not marketed. ➤ ATB: fluoroquinolones, colistin, neomycin, spectinomycin, gentamycin, apramycin in drinking water
<p>Pinworms</p>	<ul style="list-style-type: none"> • No marketing authorisation for rabbits for effective antiparasitic agents (benzimidazoles). Only flubendazole kills all stages (including eggs and larvae) of this parasite that develops in the rabbit caecum allowing 	<p>Reg</p>	<ul style="list-style-type: none"> ➤ Possible cascade use of oral available VMPs with more favorable WP since NVR: Oral flubendazole: FLIMABO and FLIMABEND – WPs for meat & offal are respectively of 3 or 4 days for pigs (depending on dosage) and of 2

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	treatment every 84 days (the rabbit pinworm cycle is about fifty days). Fenbendazole, oxfendazole e.g. do not kill eggs or small larvae and therefore requires several treatments at 42 days apart. Levamisole, widely used in the past, is no longer effective.		<p>days for chicken; => WP for rabbits ≥ 6 days</p> <p>PANACUR Aquasol 200 mg/mL - WP meat & offal of 4 days for pigs and of 6 or 9 days for chicken (depending on dosage). => WP for rabbits ≥ 9 days</p> <p>Deworming of females before weaning</p>
Staphylococci with LV strain	<ul style="list-style-type: none"> There are still a few cases that cause pododermatitis. Various strains, some close to human <i>S.aureus</i> (publications on this point). 	PhV	<ul style="list-style-type: none"> ➤ Breeding techniques: cleaning up breeding farms. Foot rests on the gratings ➤ ATB: systematic antibiogram. In general use of macrolides, tetracyclines and sulfonamides-TMP. ➤ Auto-vaccine (partial solution): no request to the ANMV registered to date.

per memento

VHD new strain	<p><i>pm: ANMV meeting with the sector on 19/03/20:</i> New variant VHD vaccines: insufficient efficacy, challenged SPC protocols and too high cost for mass vaccination in fattening units. Very tense situation with 28% of farms affected in 2018 and 26% in 2019 despite the control plan put in place. 10% of farm cessations related to VHD in 2018 and 35% in 2019.</p>	PhV	<ul style="list-style-type: none"> ➤ Temporary Authorisation for use (TAU) for vaccines (TAU renewed in Feb 2024 for Filavac VHD VAR K) were very useful to control the situation. A single injection is usually sufficient. ➤ Financial support (FMSE fund) for vaccination of fattening units. ➤ Good training of breeders to detect the first signs. ➤ Epidemiological monitoring, which is key and should be maintained, as well as biosecurity measures. <p><i>pm: 2 new vaccines are available since 2019:</i></p> <ul style="list-style-type: none"> - FATROVAX RHD KC+V 1 (Fatro) - AMM 16/08/21 - NOBIVAC MYXO-RHD plus (MSD) – MA 19/11/19 <p>ANMV info: 1 new vaccing since the last meeting: YURVAC RHD from Hipra (centralised MA on 11/09/23)</p> <p>Field info: A failure noted during an episode on Reunion Island, when Filavac VHD VAR K (under TAU) was effective => is a MA considered?</p>
Inflammation and pain	<ul style="list-style-type: none"> No VMPs with MA for rabbits. <p>Lack of data on the interest of an antiinflammatory drug in combination with antibiotic treatment and lack of treatment protocol. Off-label use of paracetamol and meloxicam.</p>	Reg	<ul style="list-style-type: none"> ➤ Cascade use of VMPs authorised for other species is now possible thanks to more favorable WP allowed by the new regulation 2019/6: <p>Paracetamol has an MRL status only for pigs and oral route (WP of 0 day for meat and offal) => possible cascade use for rabbits with WP of 1 day. Meloxicam has an MRL status in rabbits => it is not the MRL status that blocks the development of a MA. METACAM 15mg/mL Oral suspension – WP meat and offal = 3 days for horses, 5 days for pigs => cascade use possible for rabbits with WP ≥ 8 d.</p>

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			Ketoprofen: No MRLs currently required for cattle, pigs and horses. No restrictions on use. MA for oral solution with WP of 1 day for pigs (KETOPROPIG for pigs and DINALGEN for cattle & pigs) => WP of 2 days for rabbits
Staphylococci due to HV strain	There are no more cases now.	PhV	ATB, autovaccine Autovaccine (partial solution, no eradication): no request registered at ANMV to date.

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PRIORITIZATION

Prioritisation of participants (excluding ANMV)	Samuel BOUCHER	Olivier SALANDRE	Claire CHAUVIN	PRIORITIES in 2022 Major:M minor: m
Identified gaps				
Respiratory disorders due to pasteurella, mycoplasma and/or bordetella	M n°1	M n°1	M n°1	M n°1
Coccidiosis	M n°2 (more widespread)	M n°2	M n°2	M n°2
Ringworm	M n°3 (zoonosis, One health approach, uncommon but cannot be cured, refusals at slaughterhouse)	M n°3	M n°3 (lack of data and information, growing concern about antifungal resistance)	M n°3
Ear scabies	m	m	m	m
Enterotoxaemia due to <i>Clostridium perfringens</i> or <i>Clostridium spiroforme</i>				
Pinworms	Solved	Solved	Solved	
Follicular stimulation (follicular maturation)	No solution if PMSG disappears	No solution if PMSG disappears	No solution if PMSG disappears	
Staphylococci due to LV strain	Solved	Solved	Solved	
Colibacillosis due to E.coli O103 PCR <i>eae</i> positive or with lesions				
VHD new variant				
Inflammation and pain				
Staphylococci due to HV strain				

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Conclusion and changes in gaps since the last hearing in June 2022:

No significant change for:

- **Respiratory disorders:** wish for MA for a vaccine (pasteurella ± mycoplasma), or for plant-based products.
A depletion study in rabbits with tilmosin VMPs for oral use may help to define a more appropriate WP than the 63-day “cascade WP”.
- **Coccidiosis:** the past detection of residues by certain third countries with the current WPs of sulfonamide VMPs approved for rabbits has condemned their use in many farms and has directed towards the use of other anticoccidials without MA for rabbits (with a favorable "cascade WP" e.g. diclazuril). There is also interest in amprolium and the veterinarians interviewed would be willing to participate in trials to validate its safety (and efficacy) in rabbits.
- **Ringworm:** no VMP available in France with MA for rabbits for this zoonosis. Problematic because of the reject from slaughterhouses as soon as lesions are detected. It should be noted that 2 vaccines are authorised in Bulgaria with MA for rabbits (VERMET with *T.verrucosum* and *T.mentagrophytes* and ПОЛИДЕЛИДЕЛА with *T.mentagrophytes* and *Microsporum canis*).

Positive trend for:

- **Pinworms:** enough treatments available with a reasonable “cascade WP”, thanks to Reg 2019/6
- **Staphylococci due to LV strain,** thanks to the **disappearance of cases**

	Meeting of 13/06/22	Meeting of 30/04/24
Major GAPS	<ol style="list-style-type: none"> 1. Respiratory disorders due to pasteurella, mycoplasma and/or bordetella 2. Coccidiosis 3. Ringworm 	<ol style="list-style-type: none"> 1. Respiratory disorders due to pasteurella, mycoplasma and/or bordetella 2. Coccidiosis 3. Ringworm
Minor gaps	<ul style="list-style-type: none"> • Ear scabies 	<ul style="list-style-type: none"> • Ear scabies
Resolution in progress	<ul style="list-style-type: none"> • Enterotoxaemia due to <i>Clostridium perfringens</i> or <i>Clostridium spiroforme</i> • Pinworms • Follicular stimulation (follicular maturation) • Staphylococci due to LV strain • Colibacillosis at E.coli O103 PCR <i>eae</i> positive or with lesions 	<ul style="list-style-type: none"> • Enterotoxaemia due to <i>Clostridium perfringens</i> or <i>Clostridium spiroforme</i> • Follicular stimulation (follicular maturation) • Colibacillosis at E.coli O103 PCR <i>eae</i> positive or with lesions
Existing solution	<ul style="list-style-type: none"> • VHD new strain • Inflammation and pain • Staphylococci due to HV strain 	<ul style="list-style-type: none"> ☑ Pinworms. Cascade use of oral VMPs possible thanks to Reg 2019/6 ☑ Staphylococci due to LV strain. Disappearance of cases.