

Therapeutic gaps in the bee sector

Meeting of 15/10/21

Participants: Samuel Boucher (LABOVET, SNGTV beekeeping commission president), Christelle Roy (Director of GDS 19, FRGDS beekeeping veterinarian), Stéphanie Franco (Anses, Head of LNR bee health, Sophia Antipolis, veterinarian), Florentine Giraud (apiculture veterinarian, FNOSAD project manager), Lionel Grisot (veterinary practitioner in Franche Comté, apiculture veterinarian mandated for DDPP, CSMV member).

for ANMV: L. Baduel, S. Barreteau, F. Pillet, J. Bietrix, L.Fabry (Excused absent: JP Orand)

Pathology	Problem* encountered *Economic: E / Cascade: C / Other: A	Type of problem * (E/C/A)	Alternatives identified	NO therapeutic solution identified	PRIORITIES Major: M minor: m
Varroosis	<p>The list of available veterinary drugs has increased with 15 marketing authorisations (MA) in France, but:</p> <ul style="list-style-type: none"> Persistent difficulties of control and questioning the effectiveness of treatments by some users. Lack of efficacy of the authorised veterinary medicinal products (VMPs), resistance of varroa mites ? <p>RFSa bee group: see drug efficacy protocol for varroosis control. Amitraz efficiency declines is recorded by the FNOSAD for several years => resistance research? Problem because of wide use of strips (except in organic farming) that are the easiest to use but their use only at the end of the year often seems not enough.</p> <p>ANMV: the number of PhV declarations is ± stable (approximately 30/year) except in 2019 (50, with an increase in declarations from the OMAA network in AURA, stimulation of the declaration by the investigating vets that year?). No quality defects detected in the strips through the quality control plan. Difficulties in objectifying lack of efficacy (the level of pre-treatment infestation is often not known). Frequent lack of information on the conditions of application of the VMP and on other impact factors, whereas this would help to identify situations where the expected effectiveness is not achieved, and formulate recommendations for use.</p> <p>There were some cases with identification of resistance after treatment but these resistances were not always persistent.</p> <p>There are different resistance detection approaches: phenotypic or genomic method. Existing work on acaricide resistance methods. LNR: One method, based on a biological test for exposure to tau-fluvalinate and amitraze, was notably implemented by Apinov as part of an academic thesis (see publication: Almecija, 2020). A molecular method for identifying the genetic</p>	E/A	<p>APIBIOXAL administration modalities by sublimation to be reviewed (efficacy depends on the device). Varroo-eddy device from a Swiss laboratory for oxalic acid powder, but low efficacy (<50%) with APIBIOXAL (according to FNOSAD test). Interest of Swiss VARROXAL with this device => desire for a Fr marketing authorisation (MA) reported by the FNOSAD to the holder (Andermatt-Biovet). Their project is to register in some countries then apply for mutual recognition (MR) in Fr. The ANMV confirms that a MA can be granted to a veterinary medicinal product (VMP) even in the case of an active substance alone, subject, inter alia, to the approval of manufacturing process, stability studies, safety for the animal and the user and efficacy for sublimation or spraying (=Swiss MA ?) Post-meeting note: it is however mentioned in an EMA Q/A that it is preferable to have an excipient in order to make the counterpart of the title of one batch to another</p> <p>Other italian devices (Oxalika Premium* or Oxalika Pro-Easy**) refer to use with APIBIOXAL ("approved for APIBIOXAL" on their website?). *https://www.talitha-info.com/produit/sublimateur-de-lacide-oxalique-oxalika-premium-avec-contrôle-de-la-température/?lang=fr</p>		<p>M N° 1 (caramelization for APIBIOXAL by sublimation and galenic problems for VARROMED)</p>

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	<p>resistance of Varroa to fluvalinate was developed by a Spanish research team (J. Gonzalez) and was implemented at the LNR in 2021 (work as part of an internship). Work is underway to implement/develop a method for detecting Varroa's genetic resistance to amitraze (a Spanish study is also being published on the subject). The LNR is in contact with Apinov and the Spanish researchers on this subject.</p> <p>A working group (WG) of the ESA platform is interested in monitoring Varroa (and the viruses transmitted by this parasite). A focus on monitoring Varroa resistance to acaricides was proposed in the WG objectives.</p> <p>ANMV : How can we better take into account FNOSAD data in the declarations of lack of efficacy reported to ANMV? Inefficiencies well documented individually (counting and monitoring of infestation before and after treatment), but difficulties for the overall analysis: lack of data on conditions of use, number of apiaries involved in trials/drugs (to assess an incidence of inefficiencies), consideration of possible biases.</p> <p>To be able to conclude on the PhV declarations: infestation requirement before and after treatment and information on the conditions of use of the VM (including T°).</p> <p>=> Proposal to work on a list of interesting elements to report in these declarations.</p> <ul style="list-style-type: none"> • Problem with APIBIOXAL in sublimation (by professional beekeepers) => caramelization ++ every 5 administrations. Working time & risks ++ for the user (explosion for Sublimox type devices). Hence the "illegal" use of pure oxalic acid, which is also much cheaper. There are 2 MAs of oxalic acid to use in dripping, but this administration requires opening the hives, which requires more time and favourable weather. • Significant and undeclared shortages in VARROMED, especially in 2021. Another difficulty with VARROMED: numerous applications needed (=> a lot of oxalic acid administered) & inadequate designed bottle for correct and accurate administration (inappropriate tip that promotes approximations and overdoses, little visible graduation). Need to connect to another device or transfer contents. 		<p>**https://www.latiendadelapicultor.com/fr/accessoires-desinfection-ruches/oxalika-pro-easy.html</p> <ul style="list-style-type: none"> ➤ Communication to stimulate research for new drugs? ➤ Research on galenic forms better suited to the active diffusion kinetics (repeated rather than prolonged exposure to brood). Release of actives not always "repeatable" with strips. "Repidosis" device? ➤ Details on diffusion of the actives in the hive could be further investigated. A project is under consideration to evaluate and model the residue transfers of crop protection and veterinary medicinal products in the hive products as part of a collaboration between Anses of Fougères, Anses of Sophia Antipolis and LNR Santé des abeilles 		
<p>American loque</p>	<p>No drug allowed. But risks of using ATB with development of resistance and contamination of honey (residues).</p>	<p>A</p>	<p>No need for chemical drugs (tetracyclines prohibited (no MRL), inactive on spores). Satisfactory treatment by transfer, change of strains, rules of sanitary measures. Research project on vaccines could be interesting (via the queen) – see Salmela & Freitak publication,</p>		<p>m</p>

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			<p>2018 (patent application of a nordic holder) https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1005015.</p> <p>FNOSAD post-meeting note: Interest of bacteriophages ? (see publications list below)</p> <p>T. S. Brady <i>et al.</i>, 2017. Bacteriophages as an alternative to conventional antibiotic use for the prevention or treatment of <i>Paenibacillus</i> larvae in honeybee hives. <i>Journal of Invertebrate Pathology</i>, Volume 150, Pages 94-100, ISSN 0022-2011.</p> <p>SB Santos <i>et al.</i>, 2019. Identification of the first endolysin Cell Binding Domain (CBD) targeting <i>Paenibacillus</i> larvae. <i>SCI Rep.</i> 2019 Feb 22;9(1):2568. doi: 10.1038/s41598-019-39097-2.</p> <p>Note that bacteriophages are expressly named in the Appendix II of the New Regulation 2019/6 as Innovative Therapies.</p> <p>Given the uncertainties associated with the change in management of this disease in France (implementation of LSA, discontinuation of sanitary policy measures), it may one day be useful to have a drug control available provided that it is easy to use (easier than a transfer for example) and not too expensive (and with all the qualities of a drug).</p>		
European loque	No drug allowed. Cases becoming more frequent, more recurrent, or more virulent. (see ECLEA study conducted by the LNR: 2017-2019)	A	Same as American Loque		m
Nosemosis	Nosemosis with <i>N apis</i> (symptomatic) seems to have disappeared in favour of <i>N Ceranae</i> (less symptomatic, weakening factor in the context of co-exposures). Rarely diagnosed. Zootechnical measures difficult only on large bee population or reduced manpower (ditto loques). No VMPs. No MRL for Fumagiline (but not really necessary)	A	<p>Numerous biotechnical methods can be used to manage emergencies (change of queen, displacement and ventilation of the hive). No real need for VMP as it would be difficult to prescribe a treatment to fight a disease that is very difficult to diagnose, Nosema being considered by many as opportunistic. Algae polysaccharides in prevention? Interest? efficiency? https://www.sciencedirect.com/science/article/abs/pii/S0144861715006517</p>	X	m

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Viroses	<p>- DWV (Deformed Wings Virus) plays an important role in Varroa-related morbidity (associated with Varroa control). - Chronic paralysis due to CBPV Many viruses identified but often without clinical consequences. No treatment for these viroses.</p>	A	<p>Research on interfering RNA (honey MRL). Application difficulties and cost.</p>	X	m
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EXISTING solution

Resolution in progress

Colony euthanasia	<p>The only current solution is sulphur wick or vaporisation of SO₂ (or oil in Anglo-Saxon countries in particular). See Mutinelli 2020 publication (OIE journal). No worse than other chemicals? User risk? Be careful of excessive regulation or need for the presence of a vet. No official method => risks in case of outbreak of <i>Aethina tumida</i> e.g.</p>		<p>➤ Need to officially validate/approve a Good Practice guide for euthanasia of bees (consolidated protocol including the entire process: from euthanasia to the fate of dead bees, brood frames, honey and the different parts of the hive - depending on the context of euthanasia).</p>		
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Actions	Who	Due date
➤ Shortages of VARROMED to be reported to ANMV by the MA holder (MAH)	ANMV => MAH	
➤ Wish for VAROXXAL MA in Fr: info to the holder	FNOSAD, RFSA	
➤ APIBIOXAL difficulties of use by sublimation (caramelization): reporting of complaints to the MAH	Users	
➤ Pharmacovigilance declarations: reminder of requirements and useful details Communication with GT GDS France, FNOSAD and SNGTV	ANMV GDS, FNOSAD and SNGTV	
➤ Monitoring of varroa resistance to existing VMPS: contact with the epidemiological surveillance platform ?	Anses	
➤ Draft of Good Practice Guide for Bee Euthanasia	SNGTV / Anses	