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French agency for food, environmental and occupational health & safety

Investigate, evaluate, protect

Antimicrobial Resistance

Actions undertaken by the Anses (alternatives to AM)

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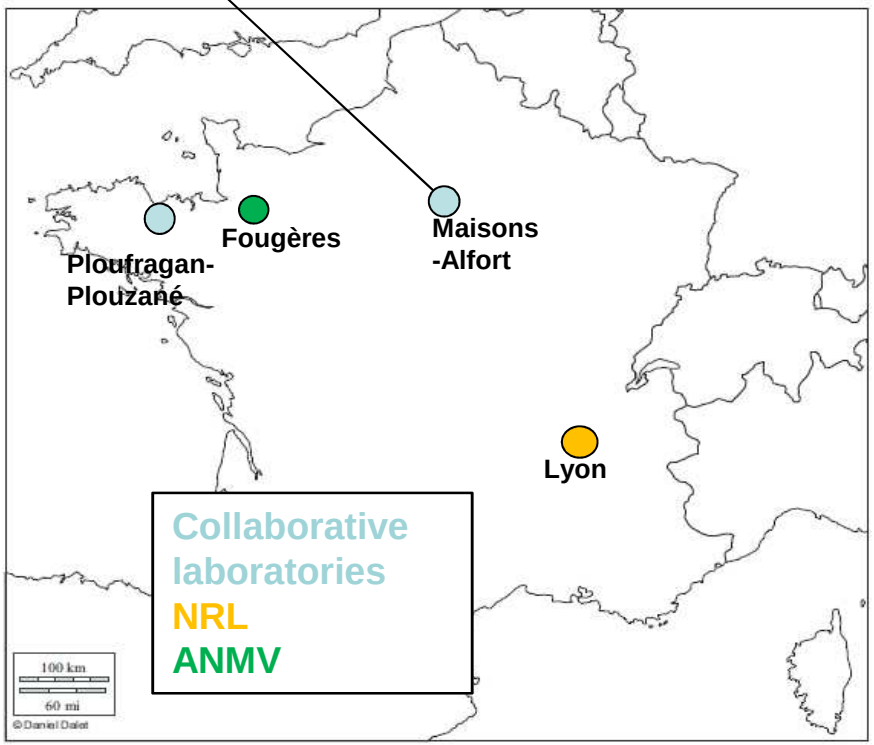
Mapping of structures involved at Anses

Coordination (Lyon) strengthened in 2015



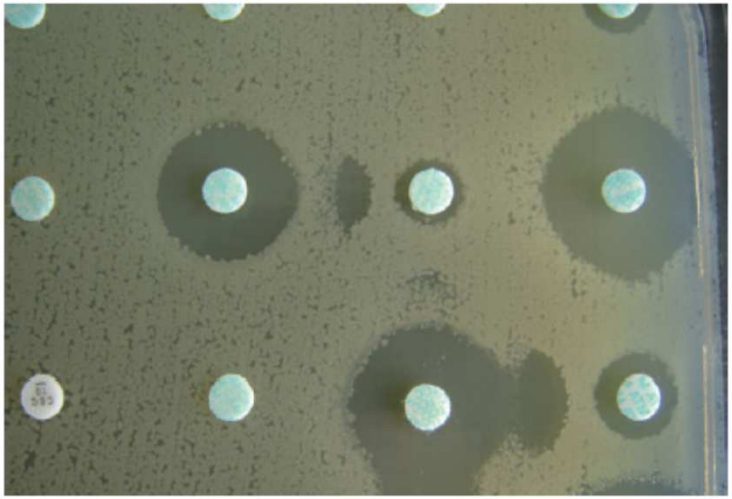
Anses laboratories and services involved in works on AMR

A historical and constant involvment

- Resapath: epidemio**surveillance** network of pathogenic bacteria from animal origin
- *Salmonella* surveillance network
- ANMV (national veterinary medicines agency, part of the Anses): **authorisations for the placing** on the market of veterinary medicines. Surveillance of quantities delivered

Focus on the Resapath and its main results

- On a voluntary basis : laboratories undertaking routine antibiograms for vets are free to join the programme and send their ATBG to Anses laboratory in Lyon for data collection:
  - **69 laboratories** (2014, increasing number)
  - and **36989** antibiograms
- All species: bovine, poultry, dogs, equidae, swine and cats by decreasing number of ATBG received)
- Identification of resistances (by species and by antibiotic)



Significant recent observations

RESAPATH, FINDINGS (2014)

- **Critical ATBQ: cephalosporins 3rd and 4th generation and fluoro quinolones**

Tendency to decrease for both ATBQ although resistances are **still highly present** e.g. 5-10% of *E. coli* in veals are R to C3G-C4G and 20% for fluoroquinolones in bovines).

- **Other ATBQ**

Constant decrease in resistances since 2006. Same for multiR: *S. aureus* resistant to meticilline (SARM) rarely observed in infectious samples in France (Equidae mainly).

- MEDICINES SALES (2015), Surveillance by ANMV and SIMV (pro. federation) **since 1999**
- Following a **recommendation by OIE in terrestrial code**
- **Declaration by labs (under AMM)**
- **Coordination by EMA**
- **Constant drop in volumes** but for 2014 in sales of antibiotics: artefact /limitation of profit margins (extra sales for storage)
  - 2013: 699 tons (-46,7% / 1999) especilaly due to 4-cyclins and sulfamides
  - Beware of interpretation (animal exposure)

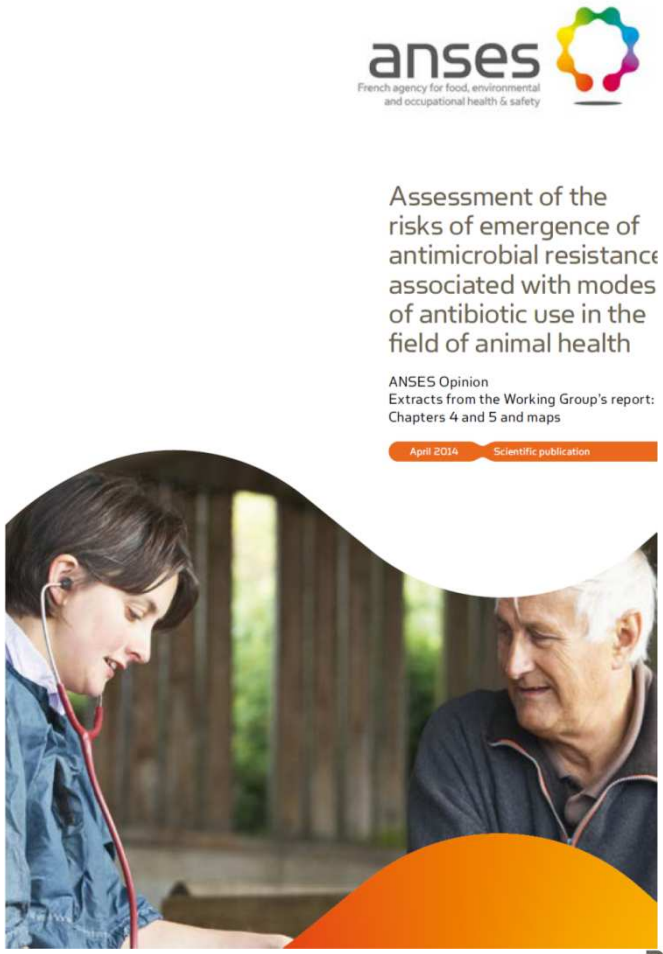
Risk assessment: opinion and report April 2014

- Questions addressed

3 committees involved: feed, animal health and veterinary medicines

« Self-request »

- 1- **State-of-the-art: use of ATBQ** by species, **inventory of existing surveillance tools** and networks, identification of **main resistances in 2012**
- 2- Assessment step: **performance of existing surveillance tools and networks**, risk **assessment for selecting resistances** (taking into account the observed patterns of use and knowledege on resistance mecanisms. Assessment of **associated risk** in public health
- 3- **Proposals and recommendations** to reduce the occurrence of resistances



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Main conclusions

opinion 2011-SA-0071

- Maintaining surveillance tools
- Mastering risky practises: including biosec./ animal genetic selection
  - No use in prevention;
  - C3 and C4G + fluoroquinolone dedicated to specific uses under strict framework;
  - Targeting of treatment: Human medicines dedicated to H; route mentioned in authorisation to be followed; use narrow spectrum ATBQ.
- Gaining better understanding through research

Assessement, what's on our agenda?

Alternatives to antimicrobial substances

Ongoing assessment (2013-SA-0122).

Measure 19 Ecoantibio programme (alternatives to AM)

1/State of the art of existing pratices and substances

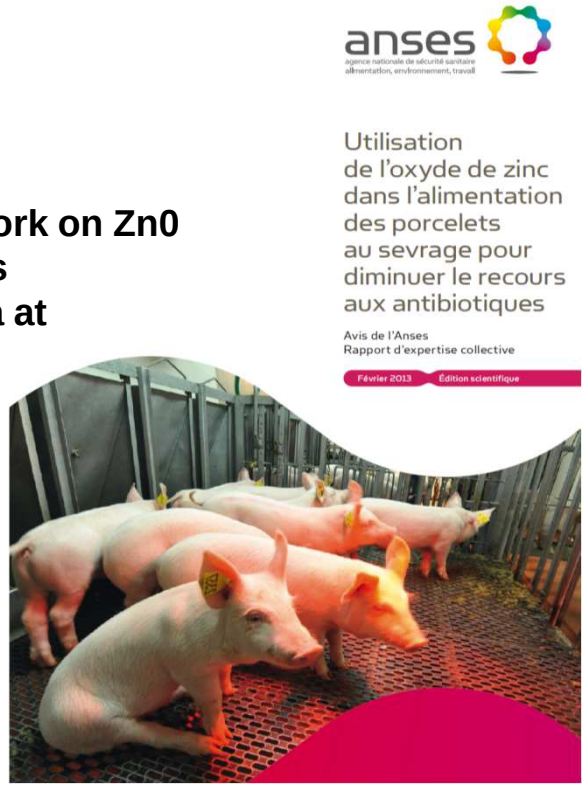
(target species and pathology of interest).

In the field survey;

2/Regulatory status of the identified substances;

3/assessment of efficacy and safety

Former work on Zn0 in pigglets (diarrhoea at weaning)



Vaccines and autovaccines
2 opinions (latest June 2016 TSE risk)

CONTEXT

- ACTION PLAN « Ecoantibio » (2013-2017) to reduce the use of antimicrobials for animals

  - **2nd axis : Develop alternatives which may lead to reduce the use of antimicrobials**

    - Measure n° 19- Assess the benefit of alternatives treatments which may lead to reduce the use of antimicrobials in animal health.

TOR n° 1

- ① Inventory of the products
  - Survey to identify :
    - Used products
    - Target species
    - Relevant diseases
    - Context of use
    - Origin of products

This survey never started :
- Too large a scope
- Too many operators, much different
- Cautious actors

Inventory by investigation of the professional press (reports of technical meetings, communications from producers, advertising, posters…) = inventory of products sold as « alternatives ».

Inventory methodology

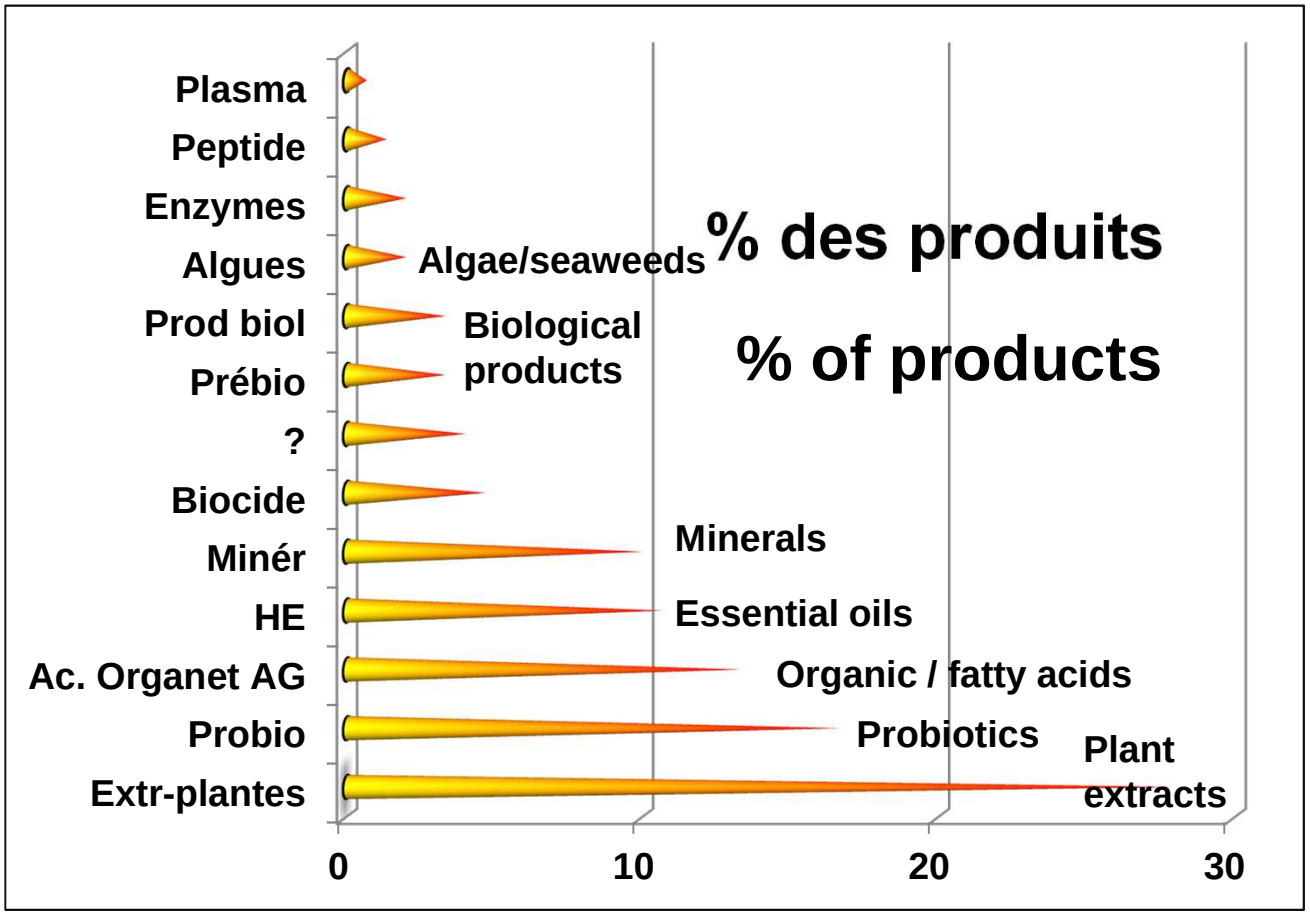
- All products that claim to be a solution to reduce the use of antimicrobials in animals
- Animal species
  - cattle,
  - poultry,
  - pig,
  - rabbit,
  - fish,
  - horse.
- Excluded :
  - Zootechnical measures and biosecurity
  - Vaccines and autovaccines

} Other groups in Ecoantibio

Inventory methodology

- Claims of an effect on animal health : health, improvement of digestive disorders, immunity, …
- No growth factors
- Claims on preventive action / stabilization / curative action
- Reports of technical meetings, communications from producers, advertising, posters…
- Websites included but not comprehensive
- Reference years : 2012, 2013 and 2014 (3 years long).

Inventory : results for simple products

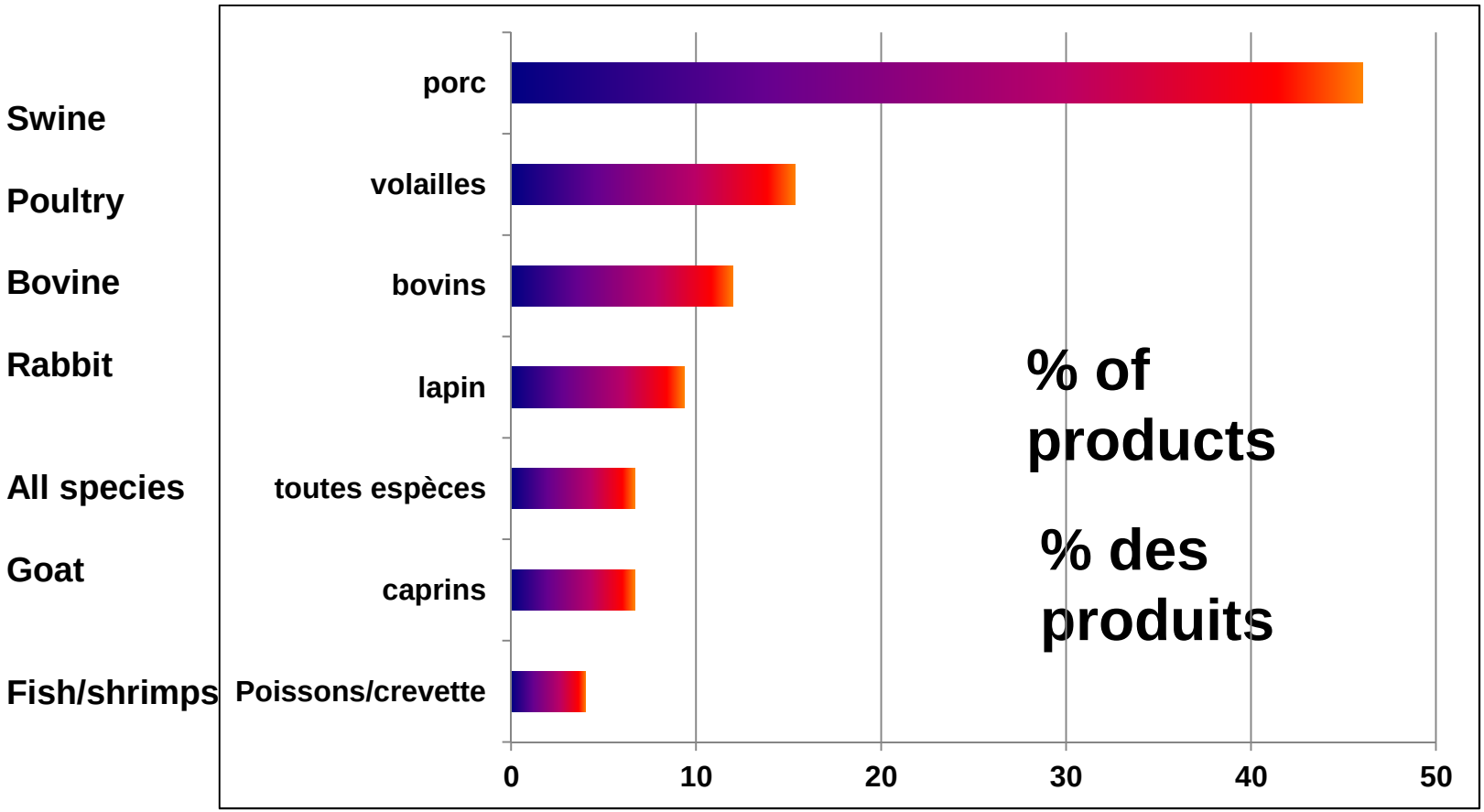


79% occurrences with 5 products*

« Products » : products categories

Inventory : results for simple products

Animal species



Limits of this inventory

- Only products cited in the professional press : proposed to veterinarians, farmers, …
- Some animal species can be less represented
- No precise composition of the products …

TOR n° 2 : Regulatory position = Is there a safety assessment ?

- Plant extracts
- Probiotics
- Organic acids
- Essential oils
- Minerals
- Prebiotics
- Algae
- Enzymes
- Peptides
- Plasma

Report on toxicological data about safety of those products, for animals, as well as for humans and the environment.

In progress

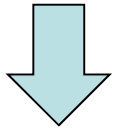
TOR n° 3 : Scientific data on efficacy

- **Step 1** : propose a methodology to assess the level of evidence of the scientific publications, which claim a role for a product, in the reduction of antimicrobial use for animals

- **Step 2** : apply this methodology to some of the product categories identified :
  - To test the method and adapt it, if necessary
  - To gather all data on each product category (metaanalysis ?)

Tor n° 3 : Methodology

1. Scientific quality of publications : building a decision tree to score the global scientific quality of publications
2. Relevance of criteria : identify and qualify the parameters used for the demonstration of the product activity, regarding a target species and a pathology



Level of evidence brought by each publication regarding the position of the product as « an alternative product to antimicrobials in animals »

Scientific quality of publications

1. Controlled experimental studies
   - Criteria ① : comparative test : experimental challenge *vs* « natural » challenge or altered breeding conditions
   - Criteria ② : comparative test using an antimicrobial *vs* the assessed product

   → Experimental design

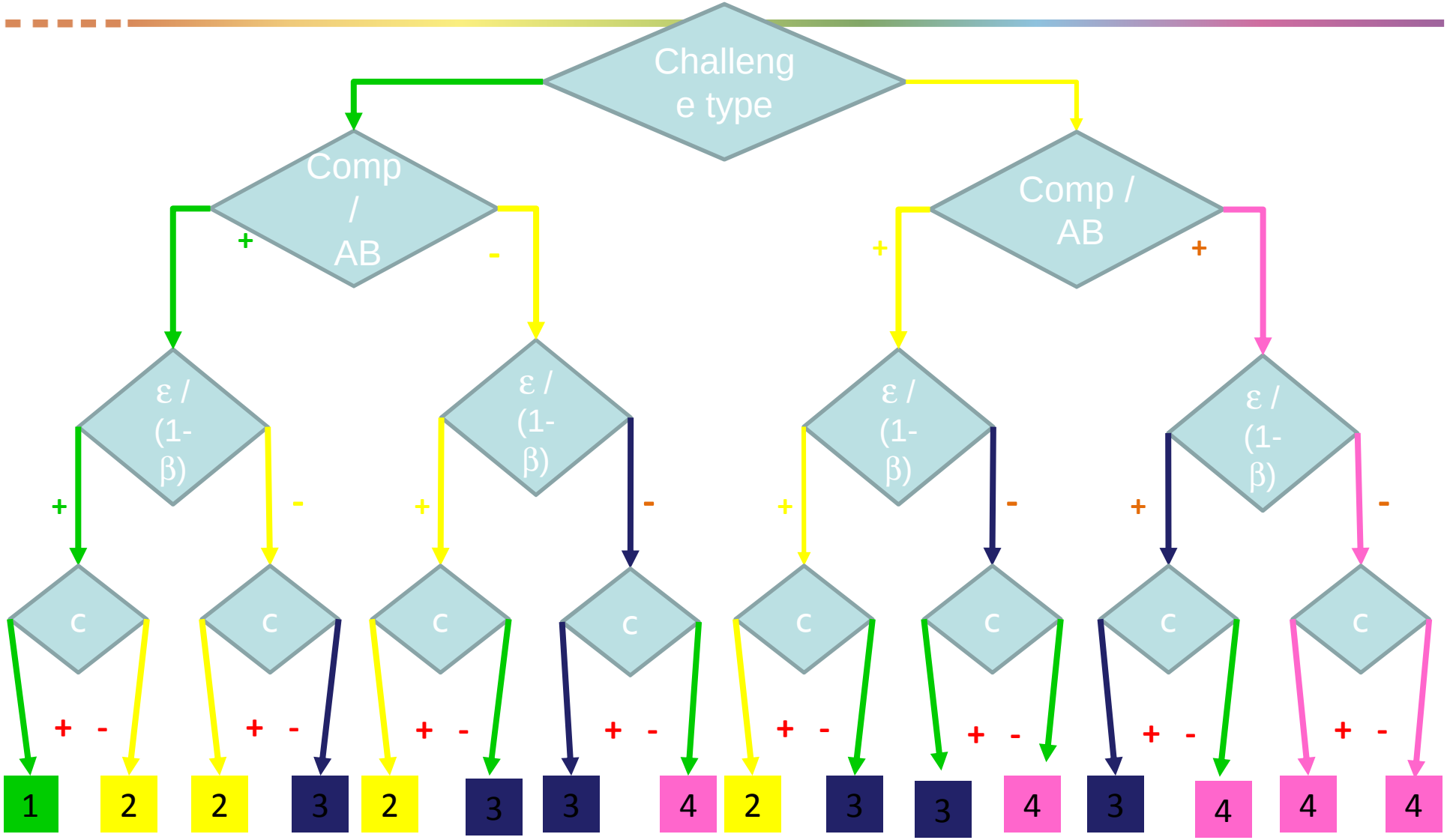
   - Criteria ③ : randomization
   - Criteria ④ : suitable statistical analysis

   → Statistical design

   - Criteria ⑤ : appropriate target species
   - Criteria ⑥: appropriate duration of the test (no disease relaps)
   - Criteria ⑦ : inoculated control actually sick

   → Test conditions

2. Epidemiological studies (in progress)


Challenge type
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Relevant criteria

Identify and qualify the parameters used in the scientific publications, for the demonstration of the product activity, regarding a target species and a pathology.

- 4 products categories as priority :
  - ✓ Plant extracts
  - ✓ Essential oils
  - ✓ Probiotics
  - ✓ Organic acids
- Animal diseases and target species :

Cattle	Young cattle	Small ruminant	Pig	Poultry	Rabbit	Fish	Horse
Salmonellosis Mastitis	Digestive disorders	Digestive disorders	Digestive disorders	Systemic colibacillosis	Digestive disorders	Systemic diseases	Digestive disorders Rhodococcosis

Parameters identified in the literature

Example with digestive disorders

Parameters	Relevance*	Parameters	Relevance*
Fecal counts of enterobacteria	++	Cytokines	+
Fecal counts of lactobacillus	+	Immunoglobulin level	0
Height of villi	++	Biochemical blood parameters	SO
Depth of crypts	++	Zootechnical parameters	+
Inflammatory cell infiltration	++	Mortality	+++
Diarrhoea stop	++ to +++	Survivor curve	+++
Clinical score for diarrhoea	+++	Cellular components from oxidative damage	0
White blood cells	0		

0 : non- relevant, + : relatively irrelevant, ++ : relevant, +++ : highly relevant, SO : purposeless

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* In discussion