

AMR – When the problem brings solutions

Javier Y. Marcos
Head of AMR & Veterinary
Products Department

Aquatic Animal Webinar Series
Alternatives to Antimicrobials & Vaccination
June 14th 2023



World
Organisation
for Animal
Health
Founded as OIE

Organisation
mondiale
de la santé
animale
Fondée en tant qu'OIE

Organización
Mundial
de Sanidad
Animal
Fundada como OIE

1940s

Thanks to **PENICILLIN**
...He Will Come Home!

**FROM ORDINARY MOLD—
the Greatest Healing Agent of this War!**

On the gauzy, green-and-yellow mold above, called *Penicillium notatum* in the laboratory, grows the miraculous substance first discovered by Professor Alexander Fleming in 1928. Named penicillin by its discoverer, it is the most potent weapon ever developed against many of the deadliest infections known to man. Because research on molds was already a part of Schenley enterprise, Schenley Laboratories were well able to meet the problem of large-scale production of penicillin, when the great need for it arose.

When the thunderous battles of this war have subsided to pages of silent print in a history book, the greatest news event of World War II may well be the discovery and development — not of some vicious secret weapon that *destroys* — but of a weapon that *saves* lives. That weapon, of course, is penicillin.

Every day, penicillin is performing some unbelievable act of healing on some far battlefield. Thousands of men will return home who otherwise would not have had a chance. Better still, more and more of this precious drug is now available for civilian use... to save the lives of patients of every age.

A year ago, production of penicillin was difficult, costly. Today, due to specially-derived methods of mass production, in use by Schenley Laboratories, Inc. and the 20 other firms designated by the government to make penicillin, it is available in ever-increasing quantity, at progressively lower cost.

Listen to "THE DOCTOR FIGHTS" starring RAYMOND MASSEY, Tuesday evenings, 8-9 P.M. See your paper for time and station.

SCHENLEY LABORATORIES, INC.
Producers of **PENICILLIN-Schenley**

2010s

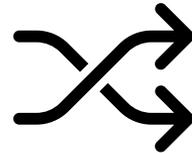
SCIENCE

Invasion of the **SUPERBUGS**

A close-up of superbug MRSA (yellow) killing a human immune cell

8 The New York Times UPFRONT UPFRONTMAGAZINE.COM

ADAPTATION

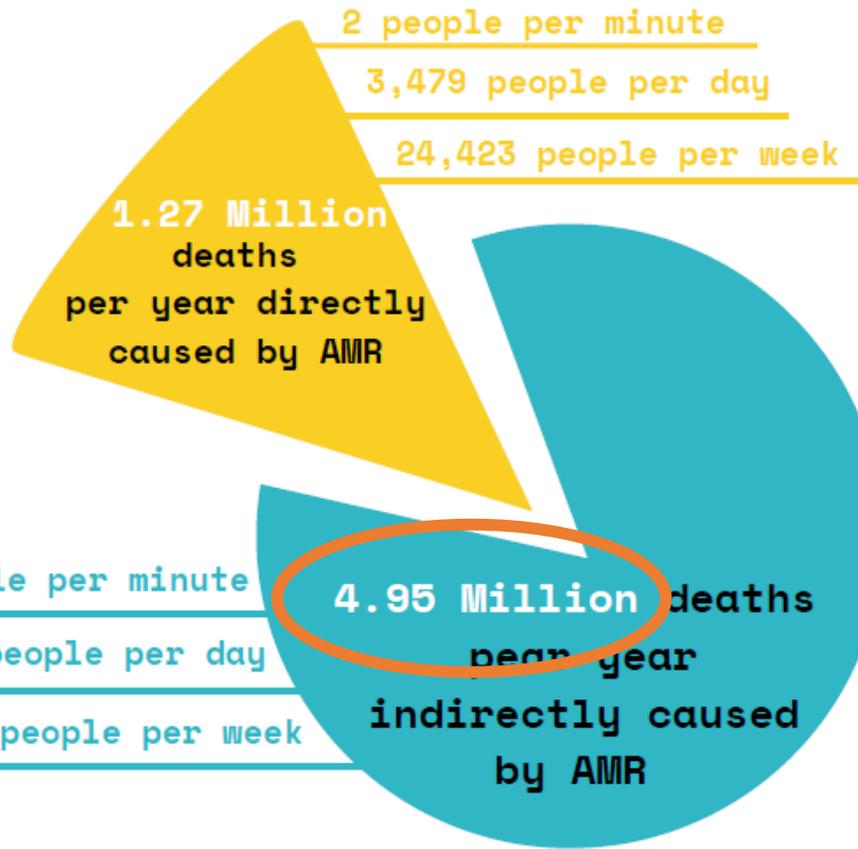


ADAPTATION



AMR – Some figures

4.95 million people died with AMR bacterial infections.
 Of these, **1.27 million** deaths were *directly* caused by AMR.



3
 2
 10
 6*

AMR is a silent pandemic

*20 million people are estimated to have died because of COVID since 2020 (WHO data – May 2023)

ACCESS



INNOVATION



CONSERVATION

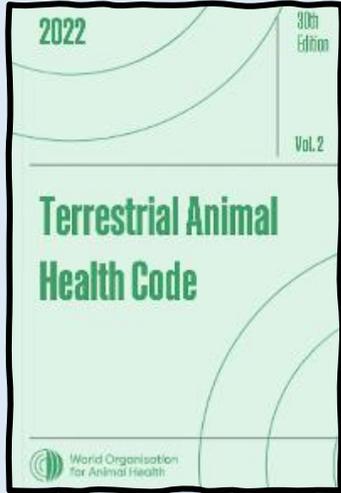
Strategies for achieving global collective action on antimicrobial resistance

Steven J Hoffman,^a Grazia M Caleo,^b Nils Daulaire,^c Stefan Elbe,^d Precious Matsoso,^e Elias Mossialos,^f Zain Rizvi^g & John-Arne Røttingen^h

Abstract Global governance and market failures mean that it is not possible to ensure access to antimicrobial medicines of sustainable effectiveness. Many people work to overcome these failures, but their institutions and initiatives are insufficiently coordinated, led and financed. Options for promoting global collective action on antimicrobial access and effectiveness include building institutions, crafting incentives and mobilizing interests. No single option is sufficient to tackle all the challenges associated with antimicrobial resistance. Promising institutional options include monitored milestones and an inter-agency task force. A global pooled fund could be used to craft incentives and a special representative nominated as an interest mobilizer. There are three policy components to the problem of antimicrobials – ensuring access, conservation and innovation. To address all three components, the right mix of options needs to be matched with an effective forum and may need to be supported by an international legal framework.



1. Responsible use



<https://www.woah.org/en/what-we-do/standards/codes-and-manuals/terrestrial-code-online-access/>

Ch.6.7. **Introduction** to the recommendations for controlling antimicrobial resistance

Ch.6.8. Harmonisation of national AMR **surveillance and monitoring** programmes

Ch.6.9. **Monitoring of the quantities and usage patterns** of antimicrobial agents used in food-producing animals

Ch.6.10. **Responsible and prudent use** of antimicrobial agents in veterinary medicine

Ch.6.11. **Risk analysis** for AMR arising from the use of antimicrobial agents in animals



<https://www.woah.org/en/what-we-do/standards/codes-and-manuals/aquatic-code-online-access/>

Ch. 6.1. **Introduction** to the recommendations for controlling antimicrobial resistance

Ch.6.2. Principles for **responsible and prudent use** of antimicrobial agents in aquatic animals

Ch.6.3. **Monitoring of the quantities and usage patterns** of antimicrobial agents used in aquatic animals

Ch.6.4. Development and harmonisation of national AMR **surveillance and monitoring** programmes for aquatic animals

Ch.6.5. **Risk analysis** for AMR arising from the use of antimicrobial agents in aquatic animals



Article 6.2.1.

Purpose

These principles provide guidance for the responsible and prudent use of *antimicrobial agents* in *aquatic animals*, with the aim of **protecting both animal and human health**. The *Competent Authorities* responsible for the registration and marketing authorisation of products and the control of all organisations involved in the production, distribution and use of *antimicrobial agents* have specific obligations.

Article 6.2.2.

Objectives of responsible and prudent use

Responsible and prudent use includes a set of practical measures and recommendations intended to **reduce the risk** associated with the selection and dissemination of antimicrobial resistant microorganisms and antimicrobial resistance determinants in *aquatic animal* production to:

- 1) **maintain the efficacy** of *antimicrobial agents* both for veterinary and human medicine and to ensure the rational use of antimicrobials in *aquatic animals* with the purpose of optimising both their efficacy and safety;
- 2) comply with the ethical obligation and economic need to **keep aquatic animals in good health**;
- 3) prevent or reduce the transfer of both resistant microorganisms and resistance determinants from *aquatic animals* to humans and terrestrial animals;
- 4) prevent antimicrobial residues that exceed the established maximum residue limit (MRL) occurring in the food.



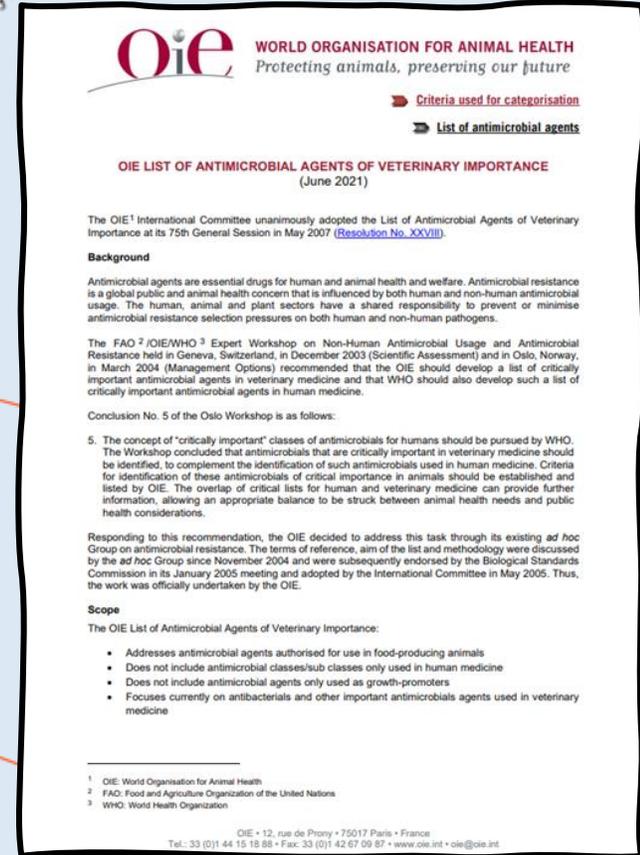
RESPONSIBLE USE - WOAH List of Antimicrobials of Veterinary Importance



WOAH's list of antimicrobials of veterinary importance

Criterion 1: Response rate of the questionnaire regarding Veterinary Important Antimicrobial Agents (more than 50% identified the importance of the antimicrobial class)

Criterion 2: Treatment essential against specific infections and lack of sufficient therapeutic alternatives



VCIA (Veterinary Critically Important Antimicrobial)

Both Criteria (1 & 2) **are met**

VHIA (Veterinary Highly Important Antimicrobial)

One Criterion (1 or 2) **is met**

VIA (Veterinary Important Antimicrobial)

No Criteria (1 nor 2) **are met**

Finalised:



Working Group on Antimicrobial Resistance - WOAH

In progress:





RESPONSIBLE USE – A word on Highest Priority Critically Important Antimicrobials

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Protecting animals, preserving our future

➤ [Criteria used for categorisation](#)
➤ [List of antimicrobial agents](#)

OIE LIST OF ANTIMICROBIAL AGENTS OF VETERINARY IMPORTANCE
(June 2021)

The OIE¹ International Committee unanimously adopted the List of Antimicrobial Agents of Veterinary Importance at its 75th General Session in May 2007 ([Resolution No. XXVIII](#)).

Background

Antimicrobial agents are essential drugs for human and animal health and welfare. Antimicrobial resistance is a global public and animal health concern that is influenced by both human and non-human antimicrobial usage. The human, animal and plant sectors have a shared responsibility to prevent or minimise antimicrobial resistance selection pressures on both human and non-human pathogens.

The FAO²/OIE/WHO³ Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance held in Geneva, Switzerland, in December 2003 (Scientific Assessment) and in Oslo, Norway, in March 2004 (Management Options) recommended that the OIE should develop a list of critically important antimicrobial agents in veterinary medicine and that WHO should also develop such a list of critically important antimicrobial agents in human medicine.

Conclusion No. 5 of the Oslo Workshop is as follows:

5. The concept of "critically important" classes of antimicrobials for humans should be pursued by WHO. The Workshop concluded that antimicrobials that are critically important in veterinary medicine should be identified, to complement the identification of such antimicrobials used in human medicine. Criteria for identification of these antimicrobials of critical importance in animals should be established and listed by OIE. The overlap of critical lists for human and veterinary medicine can provide further information, allowing an appropriate balance to be struck between animal health needs and public health considerations.

Responding to this recommendation, the OIE decided to address this task through its existing *ad hoc* Group on antimicrobial resistance. The terms of reference, aim of the list and methodology were discussed by the *ad hoc* Group since November 2004 and were subsequently endorsed by the Biological Standards Commission in its January 2005 meeting and adopted by the International Committee in May 2005. Thus, the work was officially undertaken by the OIE.

Scope

The OIE List of Antimicrobial Agents of Veterinary Importance:

- Addresses antimicrobial agents authorised for use in food-producing animals
- Does not include antimicrobial classes/sub classes only used in human medicine
- Does not include antimicrobial agents only used as growth-promoters
- Focuses currently on antibacterials and other important antimicrobials agents used in veterinary medicine

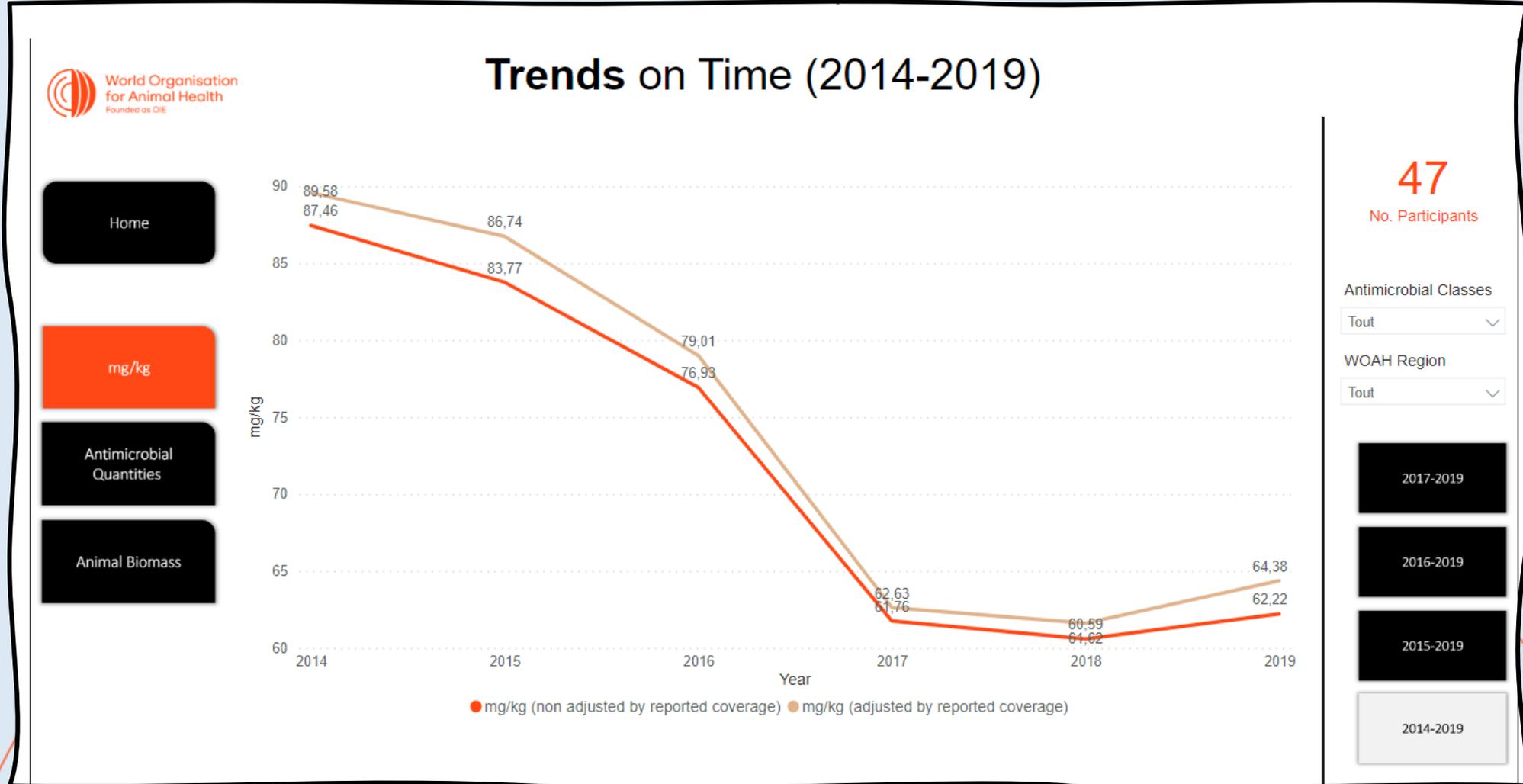
1 OIE, World Organisation for Animal Health
2 FAO, Food and Agriculture Organization of the United Nations
3 WHO, World Health Organization

OIE • 12, rue de Proby • 75017 Paris • France
Tel.: 33 (0)1 44 15 18 88 • Fax: 33 (0)1 42 67 09 87 • www.oie.int • oie@oie.int

Among the VCIA in the OIE List, some are considered to be **critically important both for human and animal health**; this is currently the case for Fluoroquinolones and for the third and fourth generation of Cephalosporins. Colistin has been moved in 2016 to the WHO category of Highest Priority Critically Important Antimicrobials. Therefore these two classes and Colistin should be used according to the following recommendations:

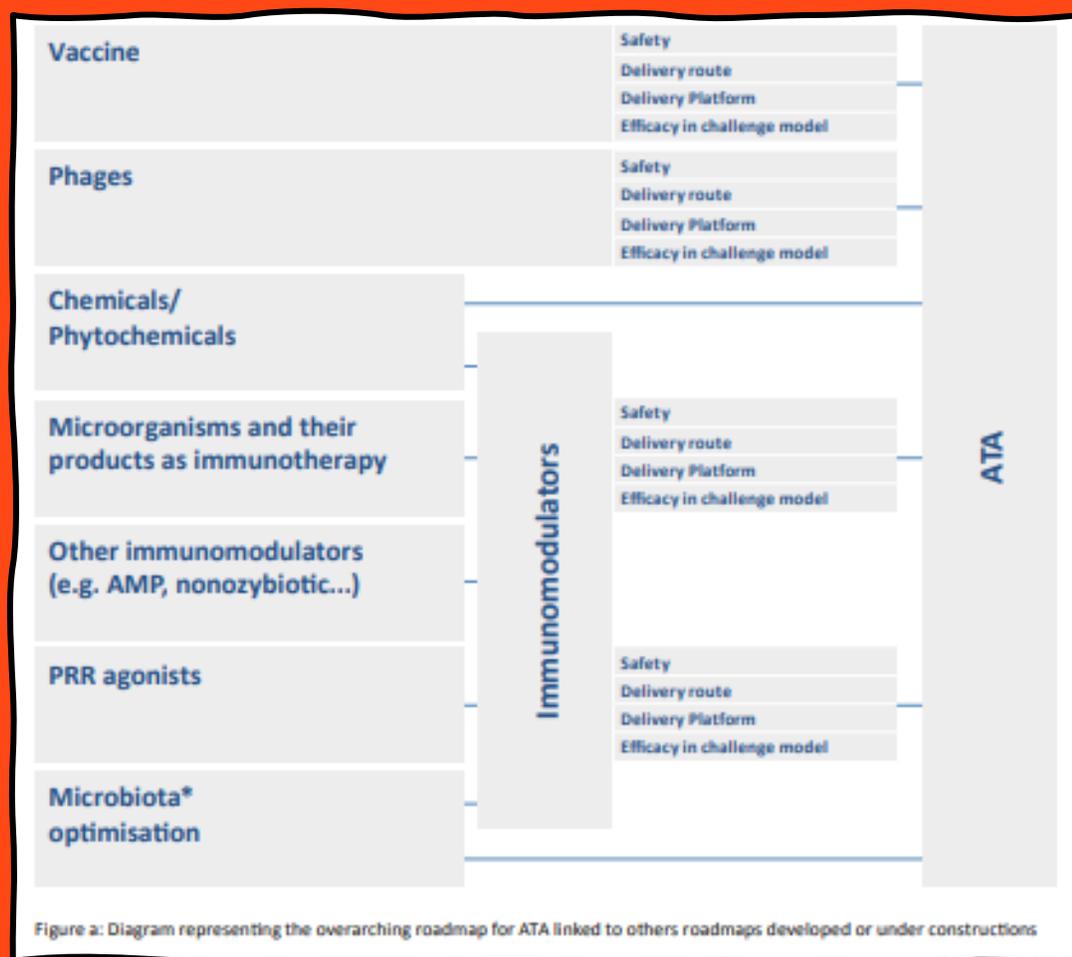
- Not to be used as preventive treatment applied by feed or water in the absence of clinical signs in the animal(s) to be treated;
- Not to be used as a first line treatment unless justified, when used as a second line treatment, it should ideally be based on the results of bacteriological tests; and
- Extra-label/off label use should be limited and reserved for instances where no alternatives are available. Such use should be in agreement with the national legislation in force; and
- Urgently prohibit their use as growth promoters.

[WOAH's list of antimicrobials of veterinary importance](#)



Since 2015, the [World Organisation for Animal Health \(WOAH, founded as OIE\)](#), has taken the lead to build a global database on antimicrobial agents intended for use in animals (AMU). In 2022, WOAHA transformed this into an online customized database system: **ANIMUSE Global Database (ANimal antiMicrobial USE)**.

2. Alternatives



The cover of the "Research Roadmap Development for Alternatives to Antibiotics Report 2022" features the STAR-IDAZ logo (International Research Consortium on Animal Health) in the top right corner. A QR code is located on the right side. The central image shows a collection of blue, white, and yellow capsules and tablets. At the bottom left, the European Union flag is displayed, and the text states: "The Secretariat for the STAR-IDAZ IRC (SIRCAH) is funded from the European Union's Horizon 2020 research and innovation programme under grant agreement No 727494".

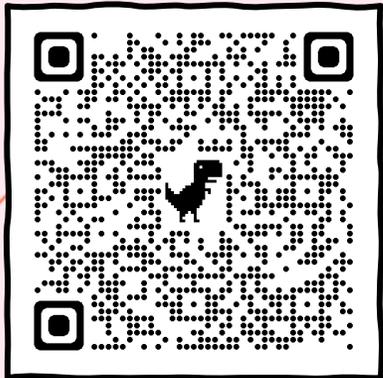


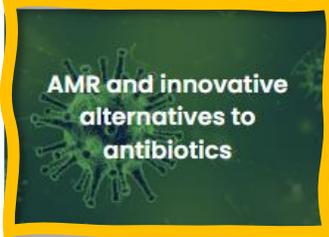
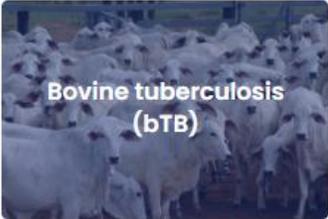
STAR-IDAZ – An International Research Consortium on Animal Health



STAR-IDAZ
International Research
Consortium on Animal Health

STAR-IDAZ International Research Consortium (IRC) is a global initiative to address the coordination of research programmes at an international level in the area of animal health and in particular infectious animal diseases including zoonoses

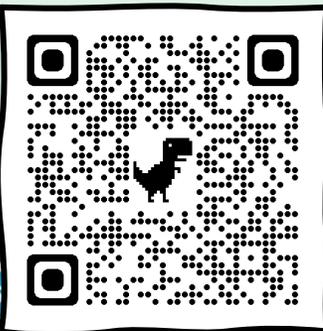


 <p>African swine fever</p>	 <p>AMR and innovative alternatives to antibiotics</p>	 <p>Animal genomics/genetics for animal health</p>	 <p>Bovine tuberculosis (bTB)</p>	 <p>Brucellosis</p>
 <p>Coronaviruses</p>	 <p>Diagnostics (tools and technologies)</p>	 <p>Emerging issues</p>	 <p>Foot and mouth disease</p>	 <p>Foresight</p>
 <p>Helminths (including anthelmintic resistance)</p>	 <p>Influenza</p>	 <p>Mastitis</p>	 <p>Mycoplasmas including CBPP/CCPP</p>	 <p>One health (including food-borne pathogens)</p>
 <p>Porcine reproductive & respiratory syndrome</p>	 <p>Porcine Respiratory Disease Complex</p>	 <p>Pox viruses</p>	 <p>Vaccinology (tools and technologies)</p>	 <p>Vector transmission and control</p>



Topic:	Research priorities
Mechanisms behind antibiotics as growth promoters:	<ul style="list-style-type: none">• Understand mechanisms of how AB work as growth promoters, to develop other alternatives• Create appropriate in-vivo/ex-vivo/in-vitro models• Basic research to better characterise microbiota• Defined standardized methods to test mechanism of subAbx and defined goal (growth vs feed conversion rate)
Phage technologies:	<ul style="list-style-type: none">• Phage-bacteria interaction• In-vivo models and trials• Investigate phage survival in the animal and in the environment• Synthetic biology for retargetable phage-based platforms• Interaction between phage and the immune system• High throughput screening platforms for phage isolation/characterisation
Immunomodulators:	<ul style="list-style-type: none">• Understand interaction between immune responses and inflammation• Mechanisms of host-microbial interaction• Kinetics and quantification of innate response stimulated by immunomodulators or by vaccines (non-specifically)• Functional studies of microbiota• Clearly define desired outcomes and best practices in testing immunomodulators
Microbiome:	<ul style="list-style-type: none">• Increase knowledge on 'the microbiome', particularly in different production forms/age-groups• Understanding mode of action of effective probiotics• Functional studies on the microbiome, linking taxonomy with function• Determine the impact microbiome shaping on vaccine efficacy and basic metabolic turnover

VACCINES – Three valuable reports worth to be rescued!



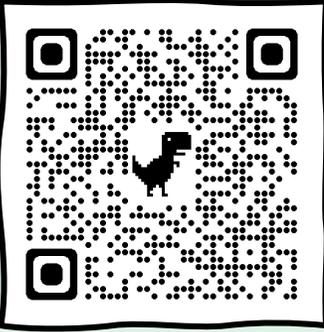
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VR VETERINARY RECORDS

REVIEW Open Access

Vaccines as alternatives to antibiotics for food producing animals. Part 1: challenges and needs

Lisa Bielke², Damer P. Blake³, Eric Cox⁴, Simon M. Cutting⁵, Bert Devriendt⁴, ...

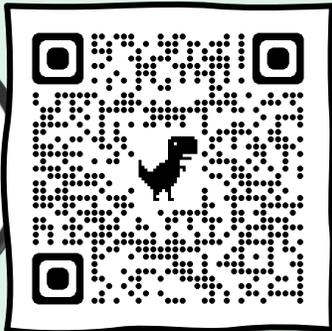


REVIEW Open Access

Vaccines as alternatives to antibiotics for food producing animals. Part 2: new approaches and potential solutions

Lisa Bielke², Damer P. Blake³, Eric Cox⁴, Simon M. Cutting⁵, Bert Devriendt⁴, ...

- ❑ Disease, antibiotic usage, availability of marketed vaccines, constraints for use or development, **priority**
- ❑ Freshwater cyprinids, marine salmonids, other marine fish, catfish
- ❑ Highest research priority assigned to
 - ❑ Freshwater cyprinids – *Aeromonas hydrophila* and other species, and *Pseudomonas* spp.
 - ❑ Marine fish - *Vibrio* spp., *Photobacterium* spp. and *Streptococcus* spp.
 - ❑ Catfish – *Edwardsiella ictaluri*, *E. tarda*, *Aeromonas hydrophila* and other species
- ❑ Research is needed on how to safely and affordably vaccines can be applied to large populations



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Protecting animals, preserving our future

Original: English
April 2015

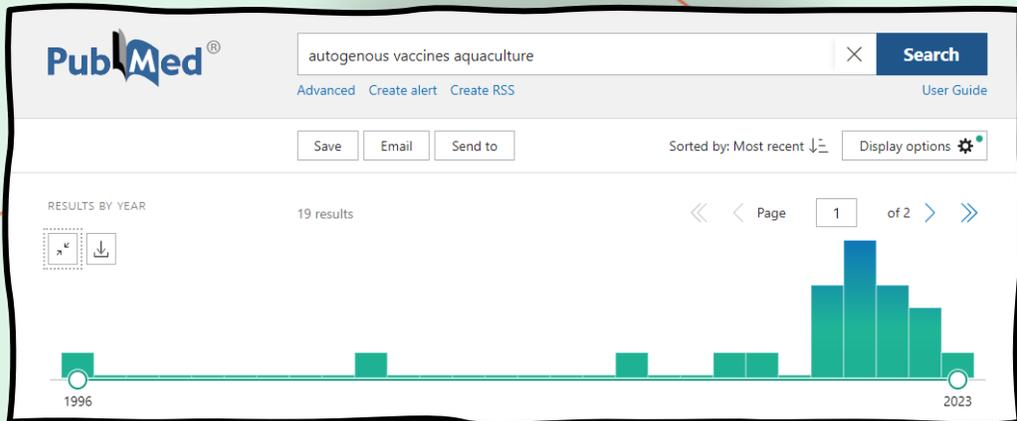
REPORT OF THE MEETING OF THE OIE AD HOC GROUP ON PRIORITISATION OF DISEASES FOR WHICH VACCINES COULD REDUCE ANTIMICROBIAL USE IN ANIMALS¹

Paris, 21 – 23 April 2015

VACCINES – What about autogenous vaccines ?



- ❑ **Autogenous (auto) vaccines are custom vaccines produced from pathogens isolated directly from affected farm(s)** on which the vaccines are subsequently deployed under a minor use or restricted permit.
- ❑ Alternative in cases where value of produced fish is low, when diversity of diseases is high, and evolution of diseases is fast
- ❑ Already used in terrestrial animals, as well as in aquatic environments
 - ❑ Atypical *Aeromonas*,
 - ❑ Novel biotypes of *Yersinia ruckeri* infections in salmonids,
 - ❑ Streptococcal pathogens in barramundi and stingrays and, in Tilapia,
 - ❑ Intracellular pathogen *Francisella noatuensis* ...
- ❑ Evidence-based formulation is critical – Enhanced diagnostics capacities
- ❑ Enable local production & blended vaccination strategies



- ❑ Very scarce scientific literature
- ❑ Currently, no international standard
- ❑ In the workplan from the AMR Working Group

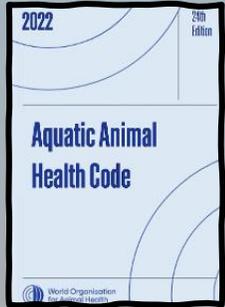
What are your thoughts ?





3. Reducing the need

- ❑ **Biosecurity** is a set of **management and physical measures** which, when used together, cumulatively **reduce the risk of infection** in aquatic animal populations within an aquaculture establishment. Planning and implementation requires identification of risks and cost-effective measures.
- ❑ The measures required will vary among aquaculture establishments, depending on factors such as likelihood of exposure to pathogenic agents, the species of farmed aquatic animal, the category of aquaculture production system, husbandry practices, environmental conditions and geographical location.
- ❑ **Chapter 4.1 (updated in 2021)** describes recommendations on biosecurity to be applied to aquaculture establishments, including semi-open, semi-closed and closed systems



Article 4.1.5.

Categories of aquaculture production systems

Article 4.1.6.

Area management

Article 4.1.7.

Transmission pathways and mitigation measures

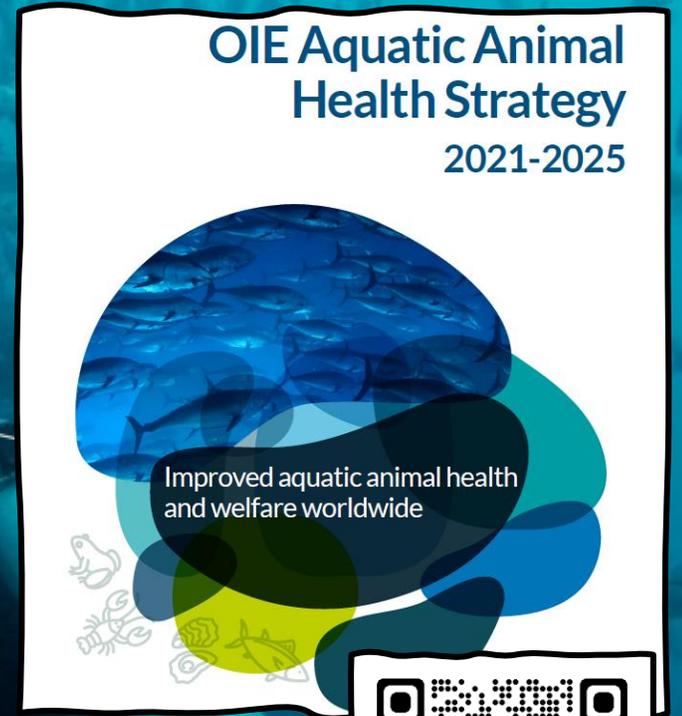
Article 4.1.8.

Risk analysis

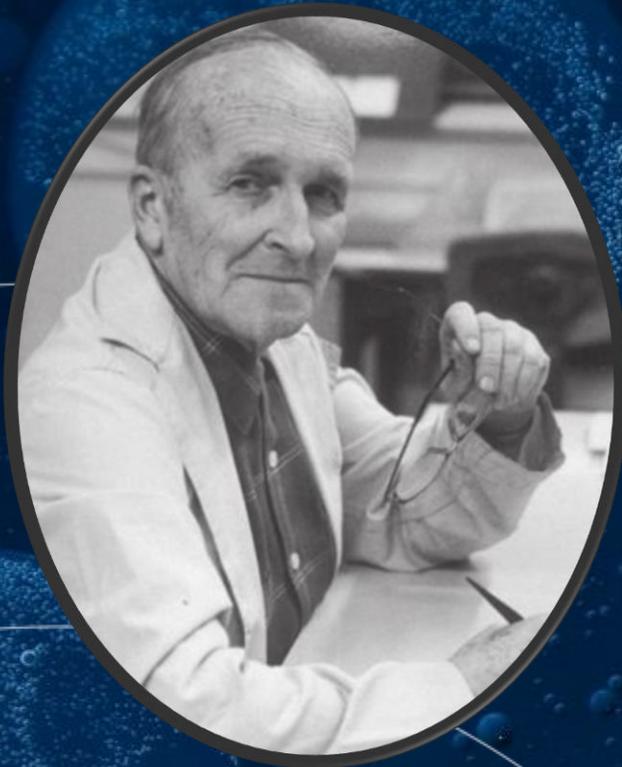
Article 4.1.9.

Biosecurity plan development

*This Aquatic Strategy is a call to action to address some of the WOAHA Community's greatest challenges in managing **aquatic animal health and welfare**. It will identify and coordinate actions that address the highest-priority common needs and focus resources on activities that will provide enduring impacts*

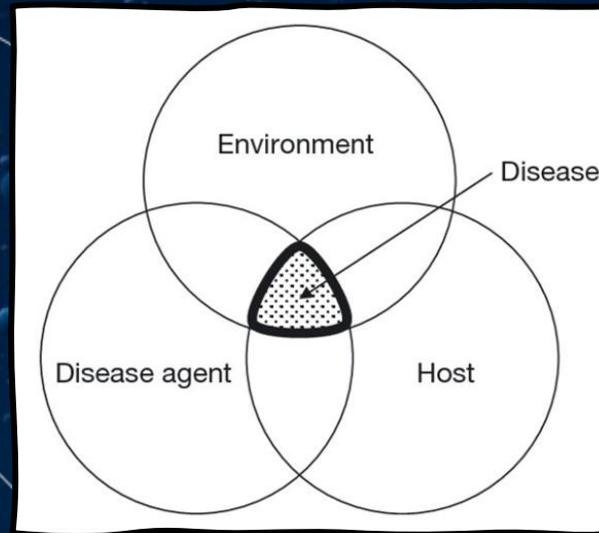


Activity 1.3 - Review the scientific basis of existing aquatic animal welfare standards. This Activity will review the science of aquatic animal welfare to evaluate whether standards continue to provide recommendations that are scientifically sound and meet the needs of Members. Priorities include assessing the developing science on sentience in aquatic animals and evaluating contemporary industry practices to promote welfare. This Activity will complement the OIE Animal Welfare Strategy and contribute to **increased understanding of aquatic animal welfare and its promotion through relevant standards.**



“Don't simply look at the pathogen as the source of the problem, but rather look at the disease as the symptom of the problem”

Dr Stalinas Snieszko (1902–1984)



Animal welfare is an integral part of animal health, and improvement measures can contribute to decreasing the need for antimicrobials. Best practices in animal welfare align with measures recognized as imperative in the fight against antimicrobial resistance.

ANIMAL HEALTH AND WELFARE AND ANTIMICROBIAL RESISTANCE AND USE

Information note of the Global Leaders Group on Antimicrobial Resistance
November 2022

GLOBAL LEADERS GROUP ON ANTIMICROBIAL RESISTANCE

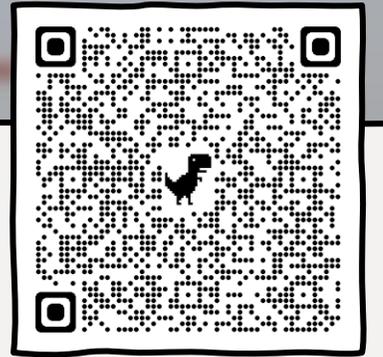
KEY MESSAGES

- Robust animal health systems, including resilient biosecurity, prevention, infection control measures and good husbandry practices are fundamental prerequisites to maintain and improve animal health and welfare. When properly designed and implemented, these measures can reduce the burden of infectious disease in animal populations and therefore dependency on antimicrobials and the risk of emergence and spread of antimicrobial resistance.**

KEY POINTS

- Strengthening animal health systems and improving professional oversight of antimicrobial use at the national level can greatly reduce the use of antimicrobials in animals.**
Guidance on appropriate and responsible antimicrobial use and better access to veterinary professionals and paraprofessionals – including those in aquatic animal health and agronomists – is needed to reduce the use of antimicrobials in animals.
Strengthening animal health systems and improving access to evidence-based treatment (e.g. clinical oversight, withdrawal periods) can assist in making informed decisions on treatments and undergo responsible antimicrobial use, ultimately leading to the reduced need for antimicrobials in animals. Strengthening animal health systems includes improving diagnostics, strengthening surveillance, quality control and access to rapid and affordable diagnostic tests for use in the field.
Ending the use of medically important antimicrobials for growth promotion is also needed to reduce the use of antimicrobials in animals.
- Effective and robust vaccination, nutrition, infection prevention and control and biosecurity measures are key building blocks to reduce the overall need for antimicrobials in farmed terrestrial and aquatic animals.**
Measures to reduce the overall use of antimicrobials include promoting and supporting disease prevention, such as vaccination programmes against major transboundary animal diseases. Vaccines have been used to control and prevent animal diseases for many years and have helped to eradicate rinderpest and limit the spread of other animal diseases such as foot and mouth disease, as well as pestiferous ruminants (PPR).





CHAPTER 1.4.

AQUATIC ANIMAL DISEASE SURVEILLANCE

Article 1.4.1.

Purpose

This chapter provides guidance on the *surveillance* approaches to be used by a *Competent Authority* to make and maintain a *self-declaration of freedom from disease* or to confirm the occurrence of a *listed disease* or an *emerging disease*.

1958

SORE THROAT?



Antibiotic Candettes give immediate soothing relief!

CANDETTES work 2 ways:

- 1 Double Antibiotic action...** fights germs! Not just one—but *two* safe, proven antibiotics kill many irritation-causing throat germs, *on contact!*
- 2 Anesthetic action...** relieves soreness! A safe and effective anesthetic acts instantly to relieve soreness of inflamed membranes.

Not an ordinary cough drop—delicious, orange-flavored Candettes are a proven medication! Get them at your drug store.

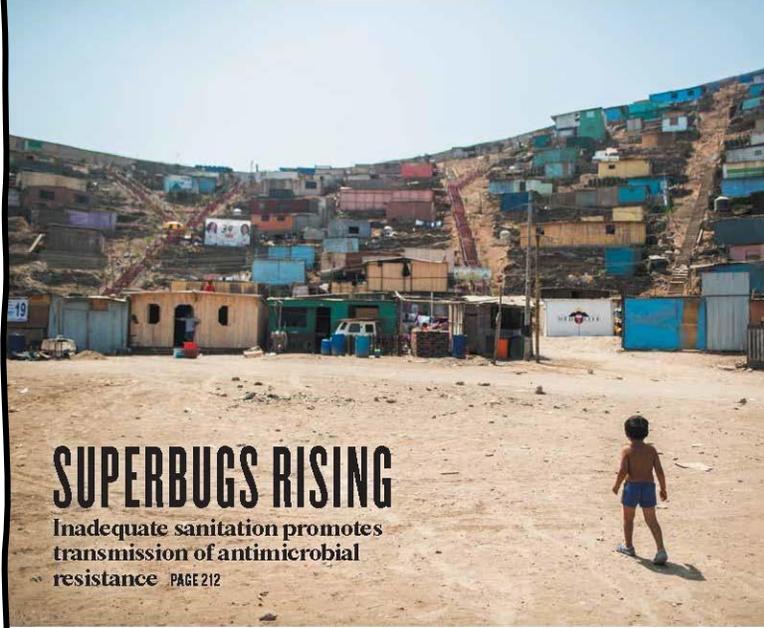


Candettes
By the World's Largest Producer of Antibiotics

ADAPTATION
↔
ADAPTATION

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SUPERBUGS RISING
Inadequate sanitation promotes transmission of antimicrobial resistance PAGE 212

CYBERSECURITY
PASSWORD PSYCHOLOGY
The human fallibility factor in cybercrime PAGE 184

HUMAN EMBRYOLOGY
THE 14-DAY QUESTION
Are research guidelines being over-taken by events? PAGES 188, 182 & 251

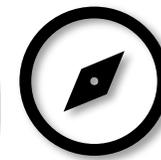
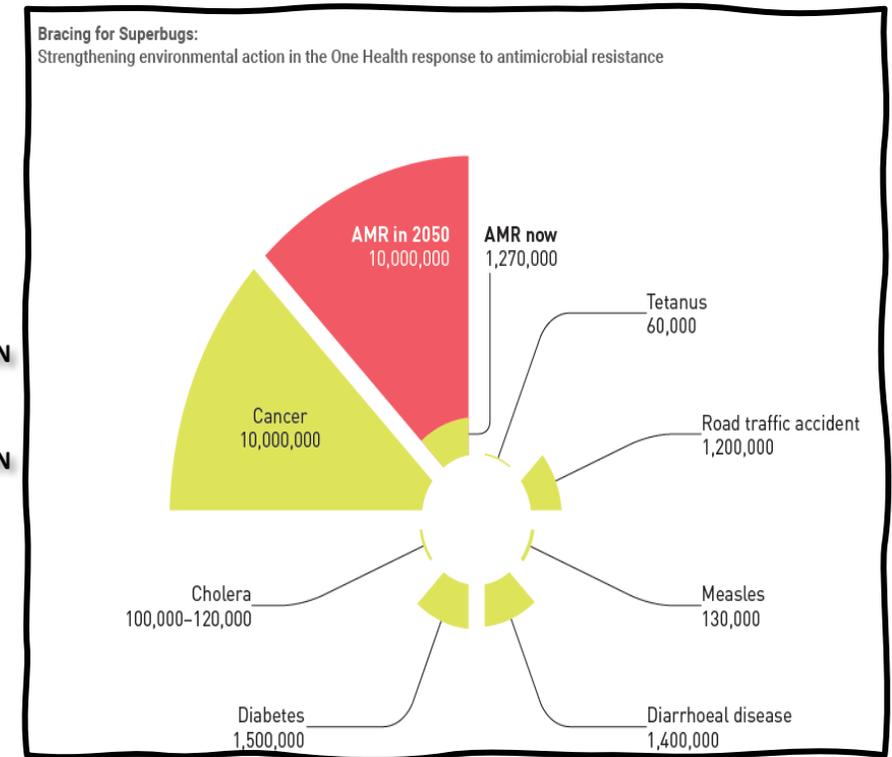
ATMOSPHERIC SCIENCE
ECHO OF AN ANCIENT AIR
Micrometeorites record high-level Archaean oxygen PAGES 184 & 235

OUTLOOK
Open innovation

NATURE.COM/NATURE
12 May 2016 \$10
Vol 533, No 7602
9 77 0028 083095

ADAPTATION
↔
ADAPTATION

2050



We can still avoid that scenario!
We need dynamic adaptation!

Gracias! Thank you! Merci!

ACKNOWLEDGEMENTS TO

- Dante Mateo
- Bernita Giffin
- Melanie Allan
- Elisabeth Erlacher-Vindel

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