Food and Agriculture Organization of the United Nations

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Brief feedback on the Gap analysis meeting for CBPP Organized by USDA-ARS and STAR-IDAZ/IRC Sanger Institute, Hinxton, UK (26– 28 June 2023)

2nd Meeting of the Standing Group of Experts (SGE) on Contagious Bovine Pleuropneumonia (CBPP) of the GF-TADs for Africa; Lusaka-Zambia (23-25 Juillet 2024)

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BACKGROUND INFORMATION

- The purpose of this gap analysis workshop was to provide current scientific knowledge of CBPP as to identify some key research gaps and recommendations to be addressed in a step wise approach.

- The workshop followed an earlier consultation (comprehensive literature review) conducted in 2023 to map the results of some of the most important mycoplasma veterinary research published over the past 10 years covering various aspects.

- The findings from this literature review have served as starting points to guide the conduct of this gap analysis meeting.

- A comprehensive report on this gap analysis meeting was published and served as the basis for this presentation.

BACKGROUND INFORMATION

➢ Organizing Bodies

The meeting was organized by the Agricultural Research Service (ARS) of the United States Department of Agriculture (USDA), in collaboration with the STAR-IDAZ International Research Consortium on Animal Health (IRC).

- **ARS:** principal in-house research agency of the USDA and aims to extend the nation's scientific knowledge with research projects in agriculture, human nutrition, food safety, natural resources, and the environment.

- **STAR-IDAZ IRC:** a global initiative aiming to coordinate research programmes at the international level and to contribute to the development of new and improved animal health strategies for priority diseases, infections, and issues.

For more information, please visit their website (https://www.star-idaz.net)

BACKGROUND INFORMATION

- **Organizing Committee:**

The meeting was organized by: Roxann Motroni (Chair of the Scientific Committee) composed of Susan Noh, Eduardo Casas, Mark Ackerman, Georgina Grell, and Madeline Newman

- **Scientific Committee:**

Rohana Dassanayake, Steve Geary, Bryan Kaplan, Lucia Manso-Silvan, Chandapiwa Marobela-Raborokgwe, Musa Mulongo, Geoffrey Muuka, Vish Nene, Robin Nicholas, Flavio Sacchini, Elise Schieck, Steven Szczepanek, Edan Tulman, and Hezron Wesonga.

- **Main objectives:**

1. provide current scientific knowledge of CBPP.
2. identify potential threats to livestock worldwide.
3. identify research needs and priorities.
4. offer an in-depth analysis of available countermeasures to contain and mitigate threats.
5. deliver specific recommendations for research and countermeasure development.

METHODOLOGY

- **Participants:** 44 participants from 28 institutions (nationals/internationals) (physically or virtually); current and retired experts experienced in the field, as well as those interested in becoming involved in the fight against CBPP.

- **Outcome expectations:** kick-start new research initiatives

- **Topics covered:** Six main research areas/topics:

- Epidemiology and Control
- Diagnostics
- Immunology
- Vaccines and Therapeutics
- Bacteriology and AMR
- Pathology and Pathogenesis.

Prior the workshop a questionnaire was completed by the interested parties to identify research gaps and priorities.

- **Group sessions:**

- 4 WGs to discuss each of the subject areas following relevant presentations using the results of the survey as a starting point.
- WGs varied during the workshop to enable free discussion.
- WG presented their research gaps during plenary sessions and identified priorities were used as basis to formulate recommendations.
- Accordingly, subject area covered was divided into 6 overlapping research areas/topics as indicated above.

OUTCOMES

The needs discussed and identified by the participants were divided into two types of gaps:

- Gaps that can be addressed by research
- Gaps for non-research that can be addressed through regulations, procedure, and policy to enhance and achieve control and eradication.

➢ **Research gaps**

They were identified for each of the **6 topics** and assessed as to whether they were short term (ST), long term (LT) or basic research (BR) as per following slides.

Note: the listed identified research gaps are not prioritized.

OUTCOMES

Session 1: Epidemiology and Control

The following key research gaps were identified based on the challenges related to:

- Lack of data on prevalence, distribution and socio-economic impact
- Evidence of the efficiency of control tools (combination of vaccination, antibiotics and movement control).

Identified research gaps in epidemiology and control:

- Investigate role for testing to detect carrier animals, for control strategy and understand the importance of carrier animals in terms of transmission.
- Improve knowledge of the distribution, prevalence, and socio-economic impact of disease (ST).
- Generate experimental evidence of efficacy for control strategies, based on combination of approaches, in an appropriate area (LT).
- Develop improved diagnostic tools for early and accurate detection including training staff to use these methods to enable capacity building (BR).
- Carry out epidemiological studies to track cattle movements in different regions of Africa, to better understand disease spread (ST).
- Assess the effectiveness of antibiotic treatments under controlled conditions including their role in continued transmission of the pathogen (ST).
- Standardize/improve control & quality of vaccines and antimicrobials, including monitoring for risk of AMR (ST).
- Investigate the potential for wildlife reservoirs such as buffalo in Kenya (ST).
- Investigate the potential role small ruminants as reservoir for CBPP.
- Obtain more data on transmission patterns between different phases of infection (especially chronic) and include up to date accurate assessment of R0 value (ST).

OUTCOMES

Session 2: Diagnostics

The following key research gaps were identified based mainly on the continuing problems with the detection of chronic/carrier animals and the availability of robust and friendly pen-side tests for both antigen and antibody.

Research gaps in diagnostics:

- Development of improved diagnostic tools for CBPP in Africa with emphasis on rapid, robust and sensitive pen-side/abattoir tests for both antigen and antibody. Assess possibility of pooling samples for more economical testing (ST).
- Develop mass screening test for obtaining seroprevalence data across Africa if supply difficulties for cELISA cannot be resolved though back-up test is desirable (ST).
- Create standardize bank of sera that can be used for verification of CBPP diagnosis (ST).
- Develop and promote use of DIVA tests to differentiate vaccinated from field infected cattle (BR).
- Develop tests for detecting all stages of the disease in particular carrier animals (BR).
- Produce antigen/nucleic acid detection kit test for the determination of accurate prevalence data (ST).
- Continue search for new disease targets to improve diagnostic tests in the long term (BR).

OUTCOMES

Session 3: Immunology

Key research gaps identified here originated from the persistent need to better understand the types of immune responses which trigger protection against CBPP.

Research gaps in immunology:

- Urgent need to improve and standardize in vivo infection models by comparing infection parameters such as aerosols, contact, intubation (ST).
- Continue development of in vitro models (tissue explants and other cellular systems) to understand early stages of infection (BR).
- Identify and differentiate B and T cell epitopes in cattle of different infection statuses (BR).
- Study and characterize adverse vaccine reactions to understand immune pathogenesis (BR).
- Reach definitions of acceptable efficacy and protection for CBPP, that are sufficient to enable other control methods to have an impact (ST).
- Identify correlates of protection for vaccine development and vaccine potency testing using transcriptomics and other tools to include protective antigens, role of antibodies, T-cell responses, biosignatures, in vitro assays, memory cells (generation and function) (BR).
- Further study host resistance linked to susceptibility and the immune response which has implication for CBPP control (BR).

OUTCOMES

Session 4: Vaccines and Therapeutics

The basis for the key gaps identified from this session was motivated by the:

- Challenges with development of vaccines with improved thermostability and long duration of immunity-DIVA
- Ongoing debates surrounding the controversial usage of antibiotic treatments.

Research gaps in vaccines and therapeutics*:

*Some of the research gaps identified under Immunology are appropriate here as well.

- Improve existing vaccine responses by comparing and optimizing new vaccination protocols (such as prime/boost), use of new adjuvants, improving thermostability and extending lifespan of the vaccine after reconstitution (ST).
- Produce better, safer more robust next generation vaccines with improved protection rate and longer duration of immunity, ideally for at least 2 years with DIVA compatibility. The availability of genome engineering techniques to generate attenuated mutants must be accelerated (BR).
- Assess and compare the different experimental challenge models to simulate more closely natural field infections with standardization of scoring schemes for use in vaccine studies (ST).
- Carry out more studies including modelling on the use of antibiotics in combination with vaccination to control CBPP while continuously monitoring for AMR of strains. The use of syndromic diagnosis may improve the effectiveness of their use (ST).
- Improve immunological and molecular understanding of the attenuation of vaccine strains and their protection. Include improved understanding of the immunology of infected vs vaccinated animals/recovered vs disease (chronic infection, death) (BR).
- Identify correlates of protection for vaccine development and vaccine potency testing using transcriptomics and other tools. To include protective antigens, role of antibodies, T-cell responses, biosignatures, in-vitro assays, memory cells (generation and function (BR).
- Continue to improve media formulations to enable greater mycoplasma yields for more efficient and

OUTCOMES

Session 5: Bacteriology and Antimicrobial Resistance

The key research gaps identified in this session originated from the need to better understand the:

- Causes (virulence factors) of persistence of mycoplasmas in the environment that contribute to the epidemiology of CBPP
- Methodologies to monitor antibiotic sensitivity in the field investigations

Research gaps in bacteriology and AMR:

- Increase understanding of AMR in *Mmm* with particular emphasis on the use of antibiotics in Africa using standardized protocols, data collection and combined with assessment of antibiotic quality in the field. Include identification of AMR genes (**ST**).
- Assess the importance of biofilms with emphasis on identifying markers particularly *in vivo*; identifying genes responsible for biofilm formation using transcriptomics; and develop MIC tests using biofilm-grown *Mmm* to determine more realistic MICs. Consider knocking out genes for biofilm formation (**BR**).
- Identify and characterize virulence factors, their genes and elucidate mechanisms of action by comparative genomics using phenotypic variants and/or across natural diversity (**BR**).
- Focus on the processes surrounding adhesion through examination of surface proteome and protective antigens (**BR**).
- Examine and compare contents of extracellular vesicles in *Mmm* with whole cells using proteomics (**BR**).
- General research on the molecular mechanisms of pathogenicity of *Mmm* and immune evasion to cover virulence factors, adhesion molecules (**BR**).
- Characterise *Mmm* tropisms, colonisation, persistence, and immune activation of ciliated and nonciliated epithelial and submucosal cell subsets of respiratory tract (including upper nasal area)

OUTCOMES

Session 6: Pathogenesis and Pathology

The key research gaps identified in this session originated from the need to better understand the mechanisms (etiopathogenesis) for the development of CBPP lesions.

Research gaps in pathology and pathogenesis:

- Verify surface-localised virulence factors, both *in vivo* and ex vivo (**BR**).
- Extensively characterize CBPP lesions using histological and immunohistochemistry of the development (kinetics) of naturally occurring disease for a better understanding of etiopathogenesis along with investigations into the kinetics of microbial colonization within the lung (**ST**).
- Generate *Mmm* mutants based on an attenuated *M. mycoides* subsp. *capri* model or CRISPR system and their testing *in vivo* as live-attenuated vaccine candidates (**BR**).
- Increase current knowledge of both local and systemic immunology following natural infection and vaccination against *Mmm*, taking advantage of multi-omics technology (**BR**).
- Study responses of respiratory epithelia to *Mmm* infection (e.g., cilia loss, necrosis/apoptosis, metaplasia) in young and adult animals (**ST**).
- Identify biomarkers that predict progression of diseases and to measure pathology (**LT**).
- Further investigate CBPP immunopathology by studying effects on host response of LppQ and

OUTCOMES

➢ Non research gaps

These were considered essential measures to be put in place through regulations, procedure, and policy to enhance and achieve control and eradication:

- Need for sustained co-operation between countries in sub-Saharan Africa to enable control of this transboundary disease.
- Standardization and harmonization of diagnostic tests across Africa with the associated requirement for training, proficiency testing and reference materials.
- General training, replacement and re-allocation of experienced staff following the pandemic, to underpin any attempts to rejuvenate and accelerate control efforts.
- Establishment of an animal identification system to enable detection of affected herds following identification in the abattoir.
- Training of staff, in particular meat inspectors, to recognize and differentiate the characteristic lesions from those caused by other respiratory pathogens,
- Standardization of protocols and establishment of controls to determine the *in vitro* MIC values of *Mmm* to antimicrobials used in the field; the establishment of strain banks and surveillance networks for AMR.
- Harmonization methods and interpretative criteria for AST.
- Consideration for connecting with existing networks such as ERFAN.

RELATED RESEARCH GAPS IDENTIFIED BY OTHER STUDIES

Other studies	Sources
- Main research gaps identified by Insight Editing 2023	- 2023 Veterinary Mycoplasmas Research Report Insight Editing London
- WOAH Standing Group of Experts (SGE) 2021	- Report of the virtual meeting of the OIE ad hoc Group on the Evaluation of CBPP Status of Members 5-7 October 2021
- Main research gaps identified by EU Discontools (2023)	- Summary of unpublished report on CBPP by DISCONTOOLS (2005)
- Main research gaps identified by CBPP Research Community (Jores et al 2020)	- Jores et al (2020): CBPP and CCPP a research community's recommendations for the development of better vaccines. Npj Vaccines 5, 66. doi: 10.1038/s41541-020-00214-2

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THANKS