AgResults Evaluation:
Brucellosis Vaccine Challenge Project
Baseline Report

Submitted to:
Department for International Development
Abercrombie House, Eaglesham Road
East Kilbride, Glasgow G75 8EA
Scotland

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Abt Associates
6130 Executive Blvd.
Rockville, MD 20852

In Partnership With:
er Guitian PhD, The Royal Veterinary College
hrist MD, S. Gilchrist Consulting Services Inc.

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Acronyms

B. melitensis	*Brucella melitensis*
BSL3	Biosafety Level 3
DALY	Disability-Adjusted Life Year
DIVA	Differentiating Infected from Vaccinated Animals
DNA	Deoxyribonucleic acid
FAO	Food and Agriculture Organization of the United Nations
GALVmed	Global Alliance for Livestock Veterinary Medicines
MVP	Minimum Viable Product
PfR	Pay for results
PM	Project Manager
R&D	Research and development

Preface

AgResults is a $147 million multilateral learning initiative. It promotes the development and dissemination of high-impact agricultural innovations for food security, health, and nutrition through the design and implementation of prize competitions that are a class of "pay-for-results" (PfR) project. AgResults also evaluates the effectiveness and efficiency of these prize competitions and incorporates evidence-based learning to refine the PfR approach.

By using PfR, AgResults goes beyond traditional aid measures to promote the adoption of innovative technologies with high-yield development impact. AgResults calls upon the ingenuity and drive of the private sector to identify and execute the most effective and efficient strategies to achieve development outcomes. It does so by providing incentives to private sector actors to develop and facilitate the uptake of innovative technologies, and overcome market failures impeding the establishment of sustainable commercial markets for such technologies or goods produced by the technologies. It thereby aims to achieve substantial and sustained development impacts, including improved food security and food safety, increased farmer incomes, and better health and nutrition.

AgResults is funded by the governments of Australia, Canada, the United Kingdom, and the United States, and by the Bill & Melinda Gates Foundation, and managed through a Financial Intermediary Fund operated by the World Bank as trustee. The AgResults team comprises the Steering Committee, Secretariat, Trustee, country-specific Project Managers (PMs), and External Evaluator. The Steering Committee oversees the implementation of AgResults and is composed of the five donors and the Trustee. The Steering Committee is responsible for strategic oversight of the initiative, including endorsement of key management decisions, approval of concepts and business plans for proposed projects, and monitoring of projects and the initiative as a whole. The Secretariat is responsible for implementing the initiative and reports to the Steering Committee. The Trustee provides financial intermediary services.

The Steering Committee appointed Abt Associates to serve as External Evaluator for AgResults. The evaluator's role is to use rigorous scientific tools to determine if the prize competitions achieve their objectives to produce private sector behaviours and social outcomes different from, and better than, what would have happened in the absence of the AgResults initiative. The evaluator defines the overall evaluation framework for the AgResults initiative and an impact analysis strategy for answering common evaluation questions for each competition. The evaluator implements and analyses field surveys, conducts qualitative market analyses, and communicates evaluation findings to the Steering Committee and wider audiences. The evaluator's role is vital to the AgResults learning agenda of understanding how donors may leverage the private sector to develop and spread agricultural innovation. As funding permits, the evaluator also assesses the sustainability of each competition's benefits once the PfR incentives are removed.

This report summarises our baseline findings and initial progress for the Brucellosis Vaccine Challenge Project. The baseline includes initial progress made because we could not conduct the baseline until competitors had applied and been accepted into the competition. Dr Judy Geyer, Dr Abigail Conrad, and Dr Luba Katz head the Abt Brucellosis Team. Dr Javier Guitian, of The Royal Veterinary College, conducts data collection and brings expert knowledge of brucellosis, its current vaccines, and its epidemiology in the developing world. Dr Shawn Gilchrist, of S. Gilchrist Consulting Services Inc., conducts data collection, and provides key inputs on the research design, combined with expert knowledge of commercial vaccine development. Dr Tulika Narayan provides overall research direction, and Cris Price leads quality assurance review of the research methods.

Executive summary

AgResults Brucellosis Vaccine Challenge Project initiative background

The AgResults Brucellosis Vaccine Challenge Project aims to use a pay-for-results (PfR) mechanism to spur the development of an improved vaccine for *B. melitensis* in small ruminants that is appropriate for use in developing countries. Brucellosis (i.e., infection of *Brucella* bacteria) is one of the world's most widespread zoonoses, which are animal diseases that are communicable to humans. While vaccines exist for *B. melitensis* (one of six *Brucella* species), they are not suitable for use in developing country contexts due in part to safety issues. The vaccines have not been modified for use in developing countries because a market for the vaccine and consequently funding are lacking. The project will award two types of milestone prizes to competitors with a total prize amount of US$30 million including a grand prize of US$20 million to the first competitor to register a vaccine that meets a specified set of characteristics.

Key Baseline Findings

Markets. The competition drew strong private sector engagement, as well as engagement from academic and public sector organizations.

Technology Adoption. Prior to the project, few advances had been made in *B. melitensis* vaccine development, although some competitors were engaged in *B. melitensis* vaccine research and development (R&D).

Cost-Effectiveness. The economic returns of the project can exceed the costs with vaccination of a small global percentage of small ruminants.

The external evaluation of this competition aims to assess whether the PfR project leads to innovation beyond what would have occurred without the project. This report presents baseline findings from the evaluation. In addition to findings on the extent to which the private sector and other sectors have engaged with the competition, the state of vaccine development prior to the project, and the extent to which economic returns to the project can exceed project costs, the report also comments on the progress of the competition in awarding the first milestone prizes. We used three primary evaluation methods to develop our baseline findings: qualitative assessment, a case comparison disease study, and cost-effectiveness simulations (see detail in Abt Associates 2016).

Baseline findings on private sector involvement

The competition drew strong private sector engagement and engagement from academic and public sector organizations. Award of the milestone 1 prize enabled competitors without existing B. melitensis *vaccine R&D projects to initiate those projects.*

In the baseline, before the competition began, the *B. melitensis* vaccine market was limited to geographic areas where control has not yet been achieved: sub-Saharan Africa, the Middle East, and parts of Asia, Latin America, and southern and eastern Europe (Spickler 2018). These markets are generally low-value markets, which reduces the incentives for vaccine development. Further, the weaknesses of the current vaccine for *B. melitensis*, Rev-

1, weaken the demand in the market, and therefore further weaken the incentive for vaccine development. A number of entities are involved in *Brucella* vaccine research, including over a dozen private companies and over two dozen public organisations. In the private sector, veterinary vaccine manufacturers are the primary actors involved in R&D on brucellosis vaccines and often collaborate with government research institutes and universities. Despite these efforts, there has been little innovation in the last 20 years. The most common *Brucella* vaccines (Rev-1 for *B. melitensis*, S2 for *B. suis*, and S19 for *B. abortus*) have been in use for half a century, and the newest *Brucella* vaccine, RB51, became available in 1996 (Yang et al. 2013).

The evaluation found evidence of a strong start to the competition in terms of private sector engagement to develop the vaccine. The majority of competitors that entered were small to medium commercial entities (10 competitors) predominantly without manufacturing experience, followed by large academic institutions (7 competitors). In addition, three public agencies entered. All but three of the competitors had past experience in *Brucella* R&D Only one competitor was a current Rev-1 vaccine manufacturer.

Three competitors withdrew in the first year of the competition. These competitors did not receive the milestone 1 prize, suggesting that either the competitors who were not awarded the prize were not very committed to the project or that a relatively small amount of funding is sufficient to stimulate initial involvement.

Baseline findings on technology innovation

Prior to the project, the competitors had made few advances in B. melitensis *vaccine development, although some competitors were engaged in* B. melitensis *vaccine R&D.*

Before the project started, some competitors had made advances with potential relevance to *B. melitensis* but were not pursuing these lines of research due to a lack of financial support. Other competitors were engaged in research that could be applied to *B. melitensis* vaccine development. The predominant challenges that competitors identified regarding *B. melitensis* vaccine development were working under BSL3 conditions,[1] securing sufficient resources to conduct R&D, and demonstrating safety and efficacy in large and expensive trials.

To help assess whether the competition leads to innovation beyond what would have occurred without the project, we assessed the level of investment in vaccine development for a set of comparison diseases. These diseases, like brucellosis, are considered neglected zoonotic diseases. To establish the baseline level of investment in the comparison diseases, we gathered information on the competitors' vaccine R&D efforts in these diseases. Of the 10 comparison diseases, competitors were working on seven of them. The majority of competitors that responded to this survey question were conducting vaccine R&D for *B. abortus,* and reported being farther along in the vaccine development process for *B. abortus* compared with *B. melitensis*. At endline, we will compare progress on these comparison diseases to the progress made on *B. melitensis* to contribute to analysis on the extent to which the prize spurred innovation beyond what would have occurred without the project. Given the complexity of factors that influence vaccine development, this comparison will help us assess whether or not vaccine development for brucellosis was part of a more common trend of vaccine development for neglected animal diseases.

[1] Biosafety Level 3 is the rating for pathogenic, potentially lethal agents (Level 4 is the highest biosafety rating). Facilities must meet a set of biocontainment precautions to handle Level 3 rated agents.

Baseline factors that may affect development impact

Experts agreed that the competition's technology specifications were well suited to address key constraints that livestock producers in low- and middle-income countries face

Starting from a baseline where no *Brucella* vaccine exists for developing country contexts, the evaluation will assess the prize competition requirements for the vaccine and whether the requirements would increase the likelihood of the vaccine's adoption in developing countries. The experts we interviewed indicated that the competition's technology specifications were well suited to address key constraints that livestock producers in low- and middle-income countries face, as they comprehensively addressed all limitations of current vaccines. Moreover, experts we interviewed agreed that a vaccine that fulfils only some of the prize requirements could still contribute significantly to *B. melitensis* control in developing country contexts.

Baseline findings on cost-effectiveness

The economic returns of the project can exceed the costs with vaccination of a small global percentage of small ruminants.

Although the vaccine has not yet been developed, and the prize competition is not aimed at increasing uptake of the vaccine, it is reasonable to assume that the vaccine would be used and health benefits realized if developed. Therefore, we conducted an *ex ante* breakeven analysis to understand the *potential* cost-effectiveness of this project. Such analysis helps determine the minimum adoption—or number of animals vaccinated—beyond which the benefits of the vaccine would exceed the cost of the competition. The benefit of developing a winning vaccine was measured as the value of the animals saved as a result of vaccination. We used the limited secondary data that was available for this analysis. Assuming a value of $28 per animal (from Rossetti et al. 2017), we estimate that if 1.2 million sheep or goats (approximately 1% of the population of sheep and goats in countries with incidence of *B. melitensis*) are vaccinated, the benefit of the project will equal its cost. Note that this vaccination rate does not indicate an optimal or recommended vaccination rate and is likely too low to result in significant human health benefits.

The breakeven analysis did not monetize and account for the benefits that are expected to result from improvements in human health associated with reduced incidence of brucellosis in animals because of the complexity in estimating these benefits at different vaccination rates. Instead, a second analysis was conducted using rates of decline in *B. melitensis* human infection, assuming a 32% and 52% vaccination rate from Roth et al. (2003). From this analysis, we estimate that the winning vaccine could save between 600,000 and 3,000,000 disability-adjusted life years (DALYs) over a 10-year period.

Baseline factors related to the sustainability of the project

The sustainability of the project will likely depend on future advocacy efforts, willingness to pay, market stability, and producer adoption.

At baseline, the evaluation considered only the factors that could influence sustainability. Interviewees reported that they expect sustainability to depend on four factors: level of awareness of the benefits of vaccination with governments and smallholders in countries

where brucellosis is endemic, the willingness of governments and producers to pay for the vaccine, market stability, and extent of producer adoption.

Early lessons learnt on the project

Early progress in the project suggests that the competition has been well received in the animal health sector and has garnered engagement from qualified competitors.

So far, the competition rules and design have been well received. The opinions the competitors have expressed about the rules and adjudication of the competition are in the majority supportive. Nevertheless, based on the evaluation findings, lessons for future projects have emerged around the following three topics:

- *Prize size*: Consider adapting the size of the prize to attract the desired applicants in the competition and adapting milestone payments to competitor types to sustain involvement in the competition.
- *Prize rules:* Consider variability in the context and policies to build flexibility into competition rules depending on the geographical location of the competitors.
- *Prize governance:* Consider adapting the selection process to improve fairness of the competition throughout the application cycle and creating clearer standards for assessing progress and awarding milestones.

1. Introduction

This report presents the evaluation findings for the AgResults Brucellosis Vaccine Challenge Project using data that were gathered after the competitors had been accepted to the competition. Therefore, the findings describe both the baseline conditions prior to the competition launch and an assessment of early participation in the project.

Brucellosis (i.e., infection of *Brucella* bacteria) is one of the world's most widespread zoonoses, which are animal diseases that are communicable to humans. Brucellosis causes impaired livestock productivity, which disproportionately affects impoverished, small-scale livestock producers (Dean et al. 2012; Corbel 2006; World Bank and TAFS Forum 2011). Two species of *Brucella* cause brucellosis in humans: *B. melitensis* and *B. abortus*, which are sustained mainly in small ruminant (sheep, goats) and large ruminant (cattle) populations (Corbel 2006). For small ruminants, *B. melitensis* (one of six species of *Brucella*) infection ranked second of all diseases considered in terms of livestock units lost worldwide (World Bank and TAFS Forum 2011). *Brucella* infection in ruminants causes economic losses due to spontaneous abortion, infertility, drop in milk production, and premature culling (Singh, Dhand, and Gil 2015).

While brucellosis can infect people through multiple routes, the key to prevention of human brucellosis is its control in livestock (Corbel 2006). Nevertheless, vaccination against this disease in small ruminants is uncommon among rural households in developing countries, due to its limited effectiveness, concerns about safety for humans and pregnant animals, and a lack of thermostability. Despite a clear need for a better vaccine against *B. melitensis*, there is little incentive for the commercial sector to invest in this area, as the expectations for return on investment are currently unfavourable.

This report is organized as follows. Section 2 presents an overview of the AgResults Brucellosis Vaccine Challenge Project and the project theory of change. Section 3 describes the evaluation purpose, questions, and methods, followed by the data sources used in Section 4. In Sections 5-10, we present the results of the assessment for each evaluation question, including the assessment of early project participation as applicable. Finally, in Section 11, we outline the next steps for the evaluation.

2. Overview of the AgResults Brucellosis Vaccine Challenge Project

This section presents the project objective and design, the project's theory of change, and the key assumptions around the theory of change that the evaluation seeks to test.

2.1 Project objective and PfR design

The project's objective is to provide incentives to develop and register a vaccine that is safe, efficacious, and viable for use against *B. melitensis* in small ruminants across the developing world. The vaccine developers can be animal health organisations, biotechnology and pharmaceutical companies, and other capable entities.

The lack of incentives for the private sector to invest in this area is the main rationale of this prize mechanism implementation. The rules of the competition were designed to provide a transparent and fair incentive to stimulate innovation.

The AgResults competition is organised in three phases or "milestones". In the first milestone, 10 applicants, called "competitors," receive a small prize of $100,000 for submitting a competitive proposal. The judging panel evaluated each application based on scientific soundness and plausibility of the proposed concept, manufacturing capabilities, and availability of animal research facilities. Then, the panel recommended one of three outcomes: (1) accepted into the next phase of the competition with a payment of $100,000; (2) accepted without payment; and (3) not accepted into the competition. While the number of entities receiving the first milestone payment was limited to 10, additional competitors could enter the competition. All entrants, regardless of milestone 1 payment, are eligible to receive subsequent prizes. .

In the second milestone, a larger prize of $1 million will be awarded to four competitors that are able to demonstrate that their vaccine meets pre-established milestone 2 requirements. The first four competitors that satisfy the requirements, as determined by the judging panel, will receive a milestone 2 prize of $1 million. A competitor may be eligible to receive a separate milestone 2 prize, for a maximum of two, if they develop another vaccine that relies on sufficiently different concepts or technologies, as determined by the judging panel.

In the third and final milestone, a single $20 million grand prize is awarded to the first competitor who registers the vaccine (milestone 3).[2] During this phase, competitors will be required to take their vaccine candidates from their milestone 2 deliverables to a registered product with a project-approved marketing authorisation. The first competitor to be granted a marketing authorisation for a vaccine, and that meet at least one of the four best-in-class requirements, will be awarded the grand prize ($20 million) and best-in-class prize ($5 million). In the event that the competitor awarded the grand prize is not also awarded the best-in-class prize, the other competitors will be entitled to this prize for up to one year following award of the grand prize.

The vaccine requirements established for the project (see Annex C for details) were meant to address many of the limitations of Rev-1, the existing vaccine, in reaching users in developing countries. To reward those able to develop an even better product, AgResults will award a $5 million prize to the first competitor that registers a vaccine that both meets

[2] The vaccine must be registered in a country that is either a current member of the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products ("VICH Country")—which includes members of the European Union, Japan, and USA—or an AgResults donor country (i.e., UK, Canada, Australia, and USA).

the MVP requirements *and* has at least one additional "best-in-class" characteristic (see Annex C for details).[3]

2.2 Brucellosis Vaccine Challenge Project theory of change

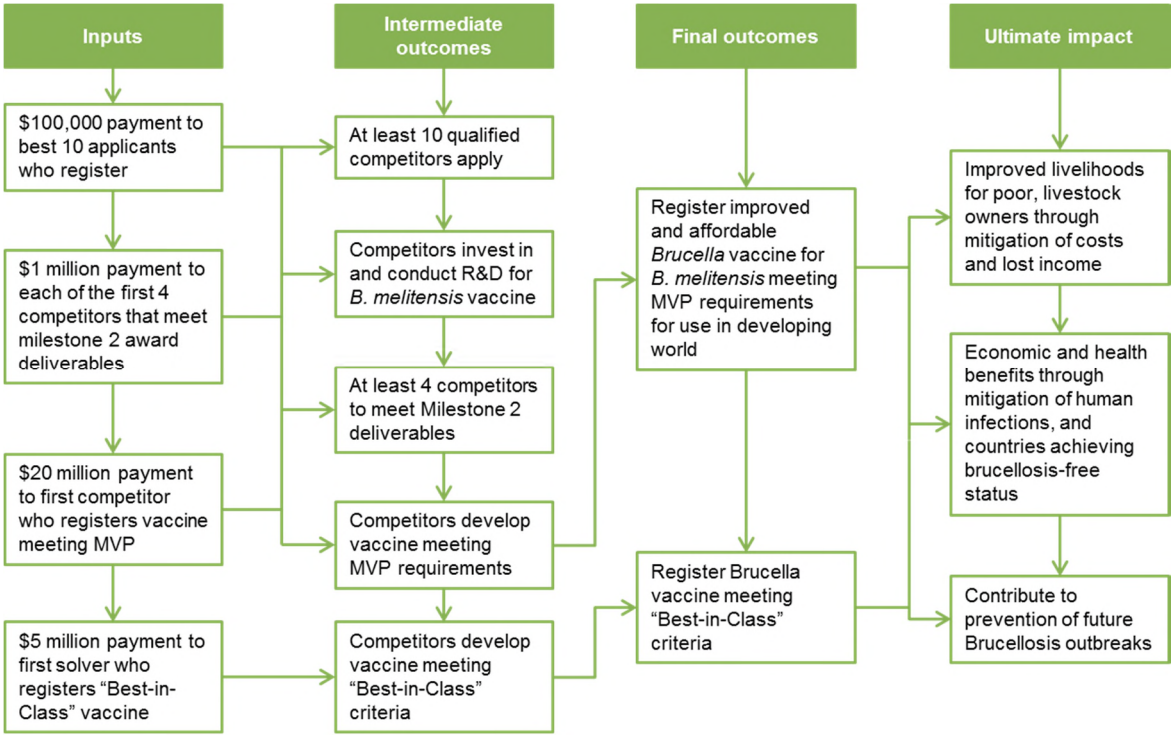
The project's theory of change reflects the causal logic by which the intervention will lead to the development of an improved vaccine for use in developing countries (Exhibit 2-1).

Economic theory and the current characteristics of the *B. melitensis* vaccine market underlie the project theory of change leading up to the development of an improved vaccine. Drawing on empirical research on prizes and economic theories, the evaluation will focus on testing the following key assumptions in the theory of change. The evaluation will do this to the extent possible given the evaluation time period, which ends before the vaccine enters distribution.

- The grand prize will motivate competitors to participate and develop an improved vaccine (Kremer and Williams 2010, Mueller-Langer 2013, Williams 2010, Fisher and Syed 2012, Berndt et al. 2007).
- Prize competitions will influence competitors by non-monetary means (Mansfield 1984; Williams 2010; Murray et al. 2012; Brunt, Lerner, and Nicholas 2008; Fisher and Syed 2012; Mueller-Langer 2013; Kremer and Glennerster 2004).
- Costs of participation will vary across competitors (Kay 2012; Boudreau, Lacetera, and Lakhani 2011).
- Certainty about prize rules and governance affects competitors' participation (Kremer and Glennerster 2004).
- The increased number of actors involved will increase the likelihood of successful vaccine development (Kremer and Glennerster 2004).
- The proposed large grand prize will limit the need for the competitor to recoup R&D costs, thereby reducing vaccine pricing.
- The grand prize will fuel diversity of product offerings and reduced vaccine prices.
- Competitors' participation in the competition may have spillover effects on related technologies.
- An improved vaccine will increase use of *Brucella* vaccines in developing countries.
- An improved vaccine will increase feasibility of mass vaccination campaigns for global brucellosis control.

Exhibit 2-1. AgResults Brucellosis Vaccine Challenge Project theory of change

[3] We note that even best-in-class product does not address all limitations of the current vaccine, such as Differentiating Infected from Vaccinated Animals (DIVA). This or other improvements may occur in the course of the AgResults competition or as a result of other R&D efforts.


Inputs
Intermediate outcomes
Final outcomes
Ultimate impact
$100,000 payment to best 10 applicants who register
$1 million payment to each of the first 4 competitors that meet milestone 2 award deliverables
$20 million payment to first competitor who registers vaccine meeting MVP
$5 million payment to first solver who registers "Best-in-Class" vaccine
At least 10 qualified competitors apply
Competitors invest in and conduct R&D for B. melitensis vaccine
At least 4 competitors to meet Milestone 2 deliverables
Competitors develop vaccine meeting MVP requirements
Competitors develop vaccine meeting "Best-in-Class" criteria
Register improved and affordable Brucella vaccine for B. melitensis meeting MVP requirements for use in developing world
Register Brucella vaccine meeting "Best-in-Class" criteria
Improved livelihoods for poor, livestock owners through mitigation of costs and lost income
Economic and health benefits through mitigation of human infections, and countries achieving brucellosis-free status
Contribute to prevention of future Brucellosis outbreaks

3. Evaluation purpose, questions, and methods

The evaluation of the AgResults Brucellosis Challenge Project, like the other AgResults project evaluations, ultimately seeks to answer questions designed to test the key components of the project's theory of change.

Broadly, the evaluation questions address private sector involvement, technology innovation, development impact, cost-effectiveness, sustainability, and lessons learnt (Exhibit 3-1). The evaluation method for this project is slightly different from that for other AgResults projects given its objective to develop technology (vaccine) and not scale up its adoption. Accordingly, the evaluation questions and the methods the evaluation employs to answer them are slightly modified. Our theory-based evaluation uses mixed methods to assess change in outcomes over time between the baseline period and the endline. To answer the evaluation questions, we use three primary evaluation methods: **qualitative assessment**, **a case comparison disease study**, and **cost-effectiveness simulations**. As shown in Exhibit 3-1, our tailored approaches for each evaluation question take into account the methodological challenges posed by an R&D, rather than an adoption project like the other AgResults Challenge Projects (see details in Abt Associates 2016).

Exhibit 3-1. Evaluation questions and approaches

#	Evaluation question[4]	Method	Data sources
1	*Private sector involvement:* What evidence exists that the project was able to stimulate private sector involvement in the development of agricultural technology/ innovation?	Qualitative assessment—private competitor motivation, decision-making, and investment in developing technology from baseline to endline	• Semi-structured interviews with competitors[5] • Small sample, structured questionnaires with competitors • Public documents and media • AgResults monitoring data and documents (e.g., competition applications, competitor entry and exit, competitor investment in R&D for competition)
2	*Technology innovation:* Did the project lead to development of new, useful technologies? What levels of innovation short of, or beyond, the specified requirements did the project lead to in the development of the technology?	Case comparison study of alternative disease[6] vaccine R&D—assessment of technology development from baseline to endline comparing progress for *B. melitensis* to that of other similar diseases along key vaccine development milestones, such as creating a lab animal model, completing an efficacy study, and registering a vaccine Qualitative assessment—success and failure in meeting MVP requirements by industry	• Semi-structured interviews with competitors and relevant experts • Small sample, structured questionnaires with competitors • AgResults monitoring data and documents

4 The evaluation questions are slightly modified from the evaluation questions in our framework to account for the project's prize competition design, which aims to only develop a technology and not scale it up.

5 In the evaluation design, we planned to also assess non-participating entities' reasons for not participating in the project. However, due to the higher than expected participation in the competition, we found it was not feasible to collect data from non-participating entities. As competitors withdraw from the project, however, we will interview them to understand their reasons for withdrawal.

6 The final set of comparison diseases are *Brucella abortus,* Q Fever, Campylobacteriosis, Enzootic abortion, Salmonellosis, Toxoplasmosis, Leptospirosis, Rift Valley Fever, Bluetongue, and Nairobi sheep disease. We considered the following criteria when selecting the comparison diseases: diseases affecting small ruminants, bacteria vs. virus or parasite, zoonosis, abortion, and limited R&D activity.

#	Evaluation question[4]	Method	Data sources
		and competitor organisational characteristics	
3	*Development impact:* What evidence exists that the project developed a technology that will have the anticipated development impact? Were the required technology specifications well suited to address the constraints expected to limit the development impact?	Qualitative assessment—actual progress and stakeholder perceptions of potential for adoption	• Semi-structured interviews with competitors and relevant experts
4	*Cost-effectiveness:* What is the evidence on the scale of any effect on private sector investment and the cost-effectiveness (relative to no intervention or traditional push mechanisms) of AgResults as a development strategy?	Cost-effectiveness simulations—calculations of the breakeven number of animal vaccinations at which the cost of the project will equal the value of saved animals and the cost of human infections averted	• Small sample, structured questionnaires with competitors • Peer-reviewed literature • AgResults monitoring and project data (e.g., governance costs, verification costs, prize amounts paid)
5	*Sustainability:* If resources and time extension to address this are provided beyond the current evaluation contract: What evidence exists that the impact of the project (e.g., private sector involvement and innovation uptake) is sustainable in the medium to long term—two years after the end of the initiative?	Qualitative assessment—actual progress and stakeholder perceptions about vaccine manufacture, sale, and adoption	• Semi-structured interviews with competitors and relevant experts
6	*Lessons learnt:* What lessons can be learnt about best practices in the design and implementation of R&D pay for results?	Synthesis of learning from other questions (integrated with learning from other technology development projects)	• Semi-structured interviews with competitors and relevant experts

4. Data Sources

This section describes the data sources and analysis used for the qualitative assessment, case comparison study, and the cost-effectiveness simulations.

4.1 Qualitative data collection and analysis

The evaluation team collected qualitative data through key informant interviews and also used project documents and secondary data sources to inform the evaluation.

Key informant interviews

The evaluation drew from 21 completed semi-structured interviews with key informants (Exhibit 4-1). This reflects the adjustments the evaluation team made to the sampling plan in the evaluation design report (Abt Associates 2016). Based on input from the Project Manager once the competitors had entered the competition, we determined it was more appropriate to interview the main point of contact at the competitor organisations, rather than respondents in a range of roles. In addition, due to the higher than anticipated interest and participation in the competition, we were unable to identify a comparable set of non-participating, capable organisations for a comparison group. As such, we interviewed only competitors and experts for the baseline.

We conducted interviews by phone in English, Spanish, and Mandarin as applicable based on the primary language of the competitors. We recorded the interviews if the respondent consented (instead taking notes if the respondent did not consent to be recorded), and then transcribed the recordings into English.

The evaluation team interviewed representatives from 12 competitors and completed these interviews in March and April 2018. By this point, three competitors had withdrawn from the competition. We interviewed them anyway to assess conditions at baseline and their participation in the project, however short. Eight competitors declined to be interviewed (six of which did not receive the milestone 1 prize). Of the eight that declined, four competitors provided brief written responses to an abbreviated set of questions in lieu of an interview.[7] Four competitors declined to be interviewed or provide written responses (one of these was a commercial entity and two were non-commercial). Through the competitor interviews, we collected data on three key factors (see Annex A for interview guide):

- Characteristics of the organisation
- Organisation's work in *B. melitensis* prior to the prize launch
- Organisation's initial participation the competition.

The evaluation team conducted interviews with eight experts in vaccine development, international development, and animal health. Experts were purposively chosen based on their area of expertise and our contacts in these communities. Through expert interviews, we collected data on their perspective on the three topics (see Annex A for interview guide):

- *B. melitensis* market
- State of vaccine R&D
- *B. melitensis* disease control.

[7] While the competition rules explain the role of the External Evaluator and encourage participation in the evaluation, they do not require competitors to share data with the External Evaluator. The Project Manager assisted with introductions to the competitors and encouraged their participation in the evaluation.

Exhibit 4-1. Qualitative sample by respondent type

Respondent type	Interviewed	Written responses	Declined
Global *Brucella* experts	8	0	3
Accepted competitors			
Accepted competitors with milestone 1 prize	8*	1	1
Accepted competitors without milestone 1 prize	3	2	2
Accepted competitors without milestone 1 prize who withdrew from competition	2	1	0
Total accepted competitors	*5*	*4*	*3*
Total respondents	**21**	**4**	**6**

*Two interviews were with representatives from the same competitor organisation.

The evaluation team analysed the interview notes, transcripts, and written responses by coding the text in NVivo using a deductively developed codebook based on the evaluation questions and topics explored in interviews. We trained coders on the codebook and provided quality review of coding, and met as a team as needed to ensure consistent application of codes. We then conducted thematic analysis to determine the patterns and variations among responses along the key themes of interest.

Document review and secondary data

The evaluation team completed a detailed review of all 20 applications of accepted competitors. We identified key fields in the applications that were of relevance to the evaluation related to competitor characteristics, and abstracted the data for those fields for each application. Then we compiled and analysed the abstracted responses in Excel.

The evaluation team also reviewed secondary data. We gathered information about the competitor organisations and their history from their websites. We also monitored the public response to the competition announcement in the media, such as news media coverage and Twitter traffic.

4.2 Competitor structured questionnaire for case comparison disease study

The evaluation also fielded a short, eight-question survey to competitors hosted on SurveyGizmo (see Annex A). A key aim of this online structured survey was to gather information for the case comparison disease study by asking competitors to report on their progress towards vaccine development for *B. melitensis* and the set of comparison diseases. We also used the survey to determine:

- Levels of investment in *B. melitensis* vaccine R&D
- Perceived feasibility of the MVP requirements
- Progress towards vaccine development for *B. melitensis* and the comparison diseases.

The evaluation team had informed the competitors we interviewed about the survey, and asked whether they agreed to participate. We solicited responses to the survey through an email request sent to the main points of contact for all 20 original competitor organisations in August 2018 and through reminder emails. Competitors responded in August and September of 2018. We received at least partial responses from 13 competitors, two of which had withdrawn by October 2018 (Exhibit 4-2). The evaluation team received five partial responses and eight complete responses. We did not require competitors to answer *all* questions, to lessen the response burden on respondents and because they may have found the financial and R&D questions sensitive. The financial and *B. melitensis* vaccine

development questions were the ones competitors most commonly skipped. We exported the data from SurveyGizmo and analysed the survey data in Excel.

Exhibit 4-2. Survey sample by respondent type

Respondent type	Complete response	Partial response	No response
Accepted competitors with milestone 1 prize	5	3	2
Accepted competitors without milestone 1 prize	2	1	4
Accepted competitors without milestone 1 prize who withdrew from competition	1	1	1
Total respondents	**8**	**5**	**7**

4.3 Cost-effectiveness study

The project will result in the potential development of a vaccine for *B. melitensis*, but the evaluation will not collect data on the number of animals vaccinated or impacts of the vaccine on human health. Therefore, it is not possible to estimate the cost-effectiveness of the investment. However, the evaluation team conducted an *ex ante* analysis of the potential benefits of the vaccine, based on assumptions about the value of the animals vaccinated, the potential risk of contracting *B. melitensis*, and the potential benefits of the vaccine to human health. This analysis was based on secondary data and assumptions from the literature; however, we note that there were very few data with which to conduct the analysis.

In particular, the evaluation team conducted a breakeven analysis to determine the number of animals that would need to be vaccinated in order for the value provided by the vaccine, or the benefits, to be equal to the cost of the project. This analysis was based on a similar approach by Rossetti et al. (2017). We also conducted an analysis of the potential reduction in human health impacts, measured in the number of DALYs that may be averted, based on data for a *B. melitensis* vaccination program in Mongolia (Roth et al. (2003).

Because many of the assumptions used in the analysis are highly uncertain, we conducted a sensitivity analysis to determine the impact of key inputs on the results. The assumptions of the analysis, including those in the sensitivity analysis, as well as the results, are discussed in more detail in Section 8.

4.4 Ethical and confidentiality considerations

To ensure that we would collect evaluation data in an ethical and responsible way, the evaluation team submitted a proposal to Abt's Institutional Review Board; but this evaluation was then exempted from the board's review.

The evaluation team obtained informed consent before collecting data. We also developed a data security plan, which we have updated as needed to track how confidential evaluation data are handled and by whom, and what security measures the study team takes to maintain respondent confidentiality. We do not attribute any responses to specific competitors in our reporting, to facilitate information-sharing and protect confidentiality.

5. Baseline Findings: Private sector involvement

Key Findings

Our baseline findings confirmed the project assumptions that a new B. melitensis is needed that is suitable for use by smallholder livestock producers. Despite this need, there has been little innovation in vaccine development for B. melitensis and the private sector does not see the market for B. melitensis *as attractive. In this context, the project has stimulated strong engagement by capable private and public sector actors on B. melitensis vaccine R&D.*

This section presents the findings for each evaluation question. The findings include the baseline findings as well as findings from early participation in the competition.

Baseline findings on private sector involvement/markets

To answer Evaluation Question 1 at baseline, we first outline the characteristics of the *B. melitensis* vaccine market to contextualise the analysis of whether the project stimulates private sector involvement at the endline. Next, we describe how the project drew entrants; the extent to which the project has stimulated entry into the competition; and the characteristics of the accepted competitors, including their baseline readiness to participate.

Vaccine market and key actors

The market for small ruminant vaccines is not as attractive as the swine, aquatics, and other veterinary markets because it is relatively smaller. The *B. melitensis* vaccine market is limited to specific geographic areas where control has not yet been achieved: sub-Saharan Africa, the Middle East, and parts of Asia, Latin America, and southern and eastern Europe (Spickler 2018). These markets are generally low-value markets, which reduces the incentives for vaccine development. Further, the weaknesses of the current vaccine for *B. melitensis*, Rev-1, weaken the demand in the market, and therefore further weaken the incentive for vaccine development.

Vaccine manufacturing is primarily done by the private sector. According to Vetvac (2010) and the Iowa State Center for Food Security and Public Health (2018), in 2018, 12 private manufacturers were producing *B. melitensis* Rev-1 vaccine in nine countries (see Annex B for list). While the current vaccine is not well suited to developing country environments, several of these private manufacturers are located in developing countries. Most developing countries where the disease is endemic rely on imports from a few main international manufacturers (Faisal Abd Al-Dayem, personal communication, 2015). In addition, government vaccine production laboratories in some countries may, more or less regularly, produce the Rev-1 vaccine for the immunisation of their national livestock (Meritxell Donadeu, personal communication, 2015). The current main buyers of the *B. melitensis* vaccine are institutions rather than individuals.

There has been little innovation in the last 20 years in vaccines for *B. melitensis* and other *Brucella* strains despite their limited suitability for developing countries. The most common *Brucella* vaccines (Rev-1 for *B. melitensis*, S2 for *B. suis*, and S19 for *B. abortus*) have been in use for half a century, and the newest *B. abortus* vaccine, RB51, became available in 1996 (Yang et al. 2013). In addition to the manufacturers of Rev-1 presented above, a number of entities are involved in research to improve the safety of the Rev-1 vaccine. The primary *public sector* actors are R&D institutions, government research institutes, government-owned vaccine manufacturers, and universities (see Annex B for list). International organisations such as the World Organization for Animal Health also participate in activities related to *Brucella* vaccines. Finally, vaccines against brucellosis in livestock are included in broader initiatives such as the Livestock Vaccine Innovation Fund. In the *private*

sector, veterinary vaccine manufacturers are the primary actors involved in R&D on brucellosis vaccine and often collaborate with government research institutes and universities (see Annex B for list).

Competition governance

This sub-section describes the competition governance to date to understand how the competition has sought to incentivise private sector engagement and competitors' experiences in the competition process. As an additional factor that influenced their participation, we also examine how the accepted competitors perceived the project.

Announcement. The AgResults Brucellosis Vaccine Challenge Project used a multi-channel strategy to publicize the competition. Competitors reported that they learned about the competition from a range of sources, indicating the benefit of a multi-channel announcement strategy. Most commonly, they reported learning about the competition in advance of the formal launch, at a conference, or through word of mouth. The competition was initially announced at the International Federation for Animal Health Conference in June 2016. The competition was further publicised in an online announcement by GALVmed and at the Brucellosis International Research Conference in New Delhi, India, in November 2016. The conference was attended by the predominant researchers in the field, meaning many potential competitors were likely in attendance and learned about the competition there. The announcement was also mentioned in technical and industry publications. Twitter traffic afterward in Europe, the United States, East Africa, and India suggested the information reached a broad audience.

Application process. Most applicants felt the burden of the application was reasonable, although a few competitors outsourced a portion of the application development. The majority of competitors we had this information for completed the application in 80 person-hours or less. This suggests that the requirements of the application process likely did not discourage interested parties from submitting an application.

Competitors' satisfaction with the application evaluation process. The majority of the competitors interviewed were satisfied (11 competitors) or somewhat satisfied (1 competitors) with the judging process (Exhibit 5-1), but a few mentioned weaknesses (3 competitors were not satisfied). Respondents who were accepted into the competition but did not receive the milestone 1 payment said that this outcome was inconsistent and that they should have been offered this small prize. Some brought up the question of fairness, noting that the early applicants faced better odds of getting the prize:

> *"The problem with the system that was adopted is that for the first deadlines the number of applications was very low and I guess it was much easier for people to get funded. We ended up in the last deadline where I think there were lots of applications and only two spots left. This is a problem because you don't have the same level of stringency along the process."*

One competitor who was awarded a milestone 1 payment cited inadequate feedback from the judging panel. Furthermore, the competitor felt the follow-up questions from the panel should have focused on the scientific concept rather than the pathway to industrialisation and registration, although manufacturing capabilities and the ability to register the vaccine are explicitly stated in the competition rules. In contrast, another competitor said that the feedback from the judges was very helpful and prompted them to re-evaluate aspects of the application.

Competitors' perceptions about the competition. In addition to satisfaction with the application process, the interviews explored the strengths and weaknesses of the prize competition to understand competitors' decision making surrounding competition entry. The competitors said that the prizes were attractive and allowed them to renew vaccine R&D efforts (Exhibit 5-1). The most commonly mentioned limitations included small (8

competitors) and uneven (8 competitors) payments, which may force some competitors to exit the competition. One competitor noted that the size of the grand prize ($20 million) was insufficient to motivate large, private sector competitors, as illustrated by the fact that only one of the top 10 companies participated. Some respondents also expressed the view that the milestones could be difficult to achieve.

Exhibit 5-1. Interviewed respondents' perceived strengths and weaknesses of the PfR competition

Attribute		Non-commercial competitors	Commercial competitors	Experts	Total
Strengths	Prizes are attractive	1	3	1	5
	Mechanism renewed research effort	1	0	3	4
	Funding allows for dedicated effort	1	0	0	1
Weaknesses	Small upfront payments	5	3		8
	Uneven disbursement of funds put ongoing effort at risk	1	5	2	8
	Milestones are difficult to achieve	0	0	1	1
	The market, not the prizes, is the incentive	0	0	1	1

Source: Interviews with or written responses from competitors (n=16) and experts (n=8).

Applicant characteristics and competition entrants

As discussed above, the prize competition was well publicised among relevant audiences and was generally viewed positively by competitors. The prize competition garnered significant interest among capable entities and stimulated a total of 39 applications. Note that we discuss the characteristics of 38 applicants in this section as organizational information was missing from one applicant. Applications were received from at least 18 countries. The majority of applications (23 of 38, or 61%) were from the Americas and Europe, where *B. melitensis* is not an issue showing that the competitors are interested in vaccine development for markets outside of their home countries.

The project received a larger number of applications that met the judging requirements than expected. As a result, the project accepted applications with the milestone 1 prize and without to allow for more participation in the competition. In all, 20 applications (51%) were accepted, half of which were awarded a milestone 1 payment and half of which were accepted without payment. Acceptance rates appeared to be higher for European and American competitors than for applicants in other regions, but the numbers were too small to draw any meaningful conclusions. It is possible that the higher participation by organisations in the Americas and Europe may influence where the vaccine is registered in the final stage of the competition, as solvers may not be familiar with the unique regulatory requirements of countries outside of their own.

The competition garnered interest from both the private and public sectors. Among the 38 competitors that had some organizational information available, 15 were commercial, 14 were academic, 8 were government-affiliated, and one had an unknown organizational type. Only two of the commercial applicants were existing Rev-1 vaccine manufacturers (one of which was accepted). Academic competitors were more likely to be accepted *and* receive the milestone 1 prize (5 of 7 accepted academic competitors versus 4 of 10 accepted commercial competitors and 1 of 8 government-affiliated organizations). At least one application was from consortiums already established between private entities and universities.

Of 39 applications received, 19 applications were declined. Among the 18 declined applications for which the evaluators had information, 2 were deemed illegitimate and 16 were rejected for lack of scientific soundness and/or manufacturing facilities. The profile of declined applicants was similar to that of the accepted applicants, both in geographical coverage and in competitor type. Applicants from Africa and the Middle East had the highest rejection rates. Commercial applications tended to be the most successful, as a group, representing 38% of all applications, but only 26% of the declined applications.

Capable non-participants

The key groups that did not apply to enter the competition were existing Rev-1 manufacturers and large veterinary health companies. Of the 12 existing Rev-1 manufacturers listed in Exhibit B-1, only two applied (and one was accepted). None of the largest veterinary health companies entered the competition as was expected. This is consistent with the literature, which shows that this type of PfR instrument tends to attract smaller, less risk-averse players rather than large commercial entities (Kay 2012).

Competitor characteristics

As presented above, three types of competitor organisations were accepted in the competition. Commercial organisations (10 organisations) represent the largest share, followed by academic organisations (7 organisations), and government agencies (3 organisations). As shown in Exhibit 5-2, the academic and public competitors tended to be larger than the commercial competitors and predominately had past experience with *B. melitensis* vaccine R&D.

Exhibit 5-2. Competitor characteristics by organization type (2017)

Competitor type	Number of R&D staff[a]	Number of full-time staff on *B. melitensis* R&D project[b]	R&D budgets[a]	Average portion of R&D budget for *B. melitensis*[c]	Prior work on *Brucella*[a, b]
Academic	130 to 9,150	3 to 8	$1-25 million: 3 competitors $26-75 million: 2 competitors >$175 million: 1 competitor	10%: 1 competitor 50%: 1 competitor 90%: 1 competitor	6 competitors
Commercial	4 to 400	0 to 5	$0: 2 competitors $1-25 million: 7 competitors Not reported: 1 competitor	≤10%: 4 competitors 20-30%: 2 competitors	7 competitors
Public agency	160 to 1,200	1 to 10	$1-25 million: 2 competitors $26-75 million: 1 competitor	80-100%: 2 competitors	3 competitors

Source: [a]Competitor applications (n=20); [b]Interviews with or written responses from competitors (n=16); [c]Competitor online survey responses (n=11)

All eight universities whose applications were accepted were large, reputable academic institutions with large faculties and well-established records in agriculture or animal health research. Overall, while all but one university was engaged in *Brucella* research prior to the competition, they were at the early stages of *B. melitensis* vaccine research projects.

The ten commercial entities accepted into the competition included 4 start-up companies, 2 contract research or manufacturing organisations, and 4 established veterinary vaccine manufacturers (two large and two small in terms of size of annual sales). Only one of these

was an existing Rev-1 vaccine manufacturer. The experience with Brucellosis vaccine R&D varied widely across these competitors, from none (3 competitors), 1 to 5 years (4 competitors), to greater than 10 years (3 competitors). The most experienced entities were established commercial manufacturers. Three commercial entities that had no *Brucella* experience believed their technologies could be extended to *B. melitensis*. For these three competitors, they reported that the competition incentivised them to engage in *B. melitensis* research for the first time and try to apply research developments from other disease efforts to *B. melitensis*.

The accepted government agencies are large animal health agencies with experience in *Brucella* research at the time of the competition.

The commercial competitors had a lower range of animal health R&D budgets than the academic and public competitors, with the majority having budgets between $1-25 million and low allocations of that budget to *B. melitensis* vaccine work. The academic and public competitors had higher ranges for their budgets and on average allocated a larger portion of their R&D funding to *B. melitensis* vaccine R&D.

The number of full-time staff working on the competitors' teams was relatively small, with a lower range for commercial competitors compared to academic and public competitors. In addition to full-time staff, the academic and public competitors generally reported that they had more part-time employees than full-time employees on their teams; however, commercial competitors did not have part-time staff on their teams.

Motivations for entry. Commercial entities predominantly were motivated by the need for funding to continue R&D (7 of 10 competitors). One competitor was interested in maintaining a leadership role in brucellosis R&D, and one considered the competition incidental to its ongoing R&D.

Universities' motivations for entering the competitions were varied, and included:

- The need for funding to pursue R&D projects
- The encouragement from a donor
- To reduce the time to take a vaccine to market
- To make a contribution to the advances in vaccine development
- To broaden the scope of R&D

Despite these differences, the potential for immediate funding appeared to be a factor in the decision to enter the competition in all cases.

The public agencies also reported varied motivations. One agency reported that they were motivated to enter the competition because they felt confident that they could win the grand prize by continuing the significant investment that they had already made in their *B. melitensis* vaccine development effort. Alternatively, another agency that is at the proof-of-concept stage reported that the competition came at an opportune time for them given that they were in the initial stages of vaccine development.

Baseline readiness of competitors. The majority of competitors that both did and did not receive the milestone 1 prize exhibited readiness to engage in *B. melitensis* R&D, which is to be expected, given the judging process applied in the competition (Exhibit 5-3). In their applications, nearly all competitors reported that they had funding available for this work or anticipate it being available, and that they have access to animal health facilities. All competitors who received the milestone 1 prize reported access to BSL3 facilities, and 7 of 10 competitors that did not receive the prize reported access. Most competitors also reported an ability to scale up manufacturing. However, a number of competitors rely on partners for their manufacturing strategy. The characteristic lacking among 70% of competitors is having authorisation/license to sell a *Brucella* vaccine prior to the competition.

Exhibit 5-3. Competitor readiness

Characteristic		Prize (n=10)			No prize (n=10)		
		Present	Absent	Unclear	Present	Absent	Unclear
Work/plan to work with partner		10	0	0	9	1	0
Funding for project available or anticipated		9	0	1	8	2	0
Access to animal research facility (incl. through partner)		10	0	0	9	1	0
Access to BSL3 facility available (incl. through partner)		10	0	0	7	3	0
Manufacturing strategy	In house	2	0	0	2	0	0
	Partner	8	0	0	4	0	0
	Both	0	0	0	4	0	0
Ability to scale up manufacturing		8	2	0	10	0	0
Authorisation/license to sell *Brucella* vaccine		3	7	0	3	7	0

Source: Competitor applications (n=20).

Competitor withdrawals. A total of three competitors had withdrawn from the competition at the time of baseline data collection. Of the six commercial competitors that were not awarded the milestone 1 payment, two ceased the development of a *B. melitensis* vaccine within the first year and withdrew from the competition. One academic competitor that was not awarded the payment also terminated the project. These three competitors reported that they withdrew from the competition due to a lack of funding because they did not receive the milestone 1 prize. These results suggest that these competitors were not very committed to the project, or that the prospect of the relatively small milestone 1 prize amount was sufficient to stimulate initial involvement.

6. Baseline Findings: Technology adoption

Key Findings

We found that most competitors were continuing to develop concepts that pre-dated the prize and were still at early stages of vaccine development—the proof of concept and vaccine characterisation stages. However, for competitors without previous B. melitensis *activity, the prize was fundamental to initiating work on this disease.*

To answer Evaluation Question 2 at the baseline, below we establish the state of *B. melitensis* R&D prior to the project, against which we will compare progress at endline. We characterise the stage of R&D achieved by competitor organisations prior to competition entry and challenges faced in *B. melitensis* vaccine development. Then, we outline the baseline status of the case comparison disease exercise, which the evaluation will use to help determine whether the competition spurred innovation and development that would not have occurred without AgResults. Lastly, we describe early developments that competitors have reported since entering the competition.

State of R&D prior to prize involvement

There has been little innovation in *B. melitensis* vaccine development in recent years. For many years, commercial entities, universities, and government R&D bodies have been aware of the limitations of existing *B. melitensis* vaccines. Progress in *Brucella* control in high-income countries during the last few decades has resulted in a gradual decline in research activity since the 1960s or 1970s, with some groups responsible for key developments in this area shifting their focus to other, more relevant pathogens. At the same time, research on *Brucella* became more prominent in countries where this disease was endemic, such as Argentina, China, and Mexico.

Before the prize was announced, research programs in brucellosis included those aimed at better characterising host–pathogen interactions and developing diagnostic tests that could differentiate between vaccinated and naturally infected animals. Some commercial entities had been exploring aspects of vaccine stability, of relevance for the commercialisation and use of the vaccine in settings where maintaining the cold chain is challenging. Some competitors working on vaccines against *Brucella abortus* or *Brucella ovis* had made advancements with potential relevance to *melitensis*, but were not pursuing these lines of research due to lack of financial support. Other competitors were engaged in research on pathogens other than *Brucella*, which could also be applied to the *B. melitensis* vaccine development. One of the approaches being explored by some research groups to address the key challenge of maintaining protection while ensuring safety was the deletion of genes to decrease the virulence of *Brucella*. This line of work was already ongoing before the prize was announced but in some cases with unclear prospects due to funding uncertainty.

R&D challenges. According to interviewees, the main obstacles to *B. melitensis* vaccine development were related to the uncertainty of the market, due to lack of awareness of *B. melitensis*, ability of individuals or governments to pay, acceptance of novel constructs, infrastructure to store and distribute a vaccine requiring a cold chain, and other problems. However, it was predominantly experts and not competitors who raised this concern. Amongst competitors, the predominant challenges were working under BSL3 conditions, securing sufficient resources to conduct R&D, and demonstrating safety and efficacy in large and expensive trials (Exhibit 6-1).

Exhibit 6-1. Interviewed respondents' identified challenges with brucellosis vaccine R&D

R&D challenge	Non-commercial competitors	Commercial competitors	Experts	Total
Uncertainty about demand for vaccine	0	2	6	8
Working in BSL3 conditions	1	3	1	5
Securing funding	2	2	0	4
Securing animal facilities for testing	1	1	2	4
Demonstrating safety and efficacy	1	2	0	3
Finding an industry partner	1	2	0	3
Achieving a low price	1	1	0	2
Antigen discovery/screening	1	1	0	2
Expressing of antigen in sufficient quantity	0	2	0	2

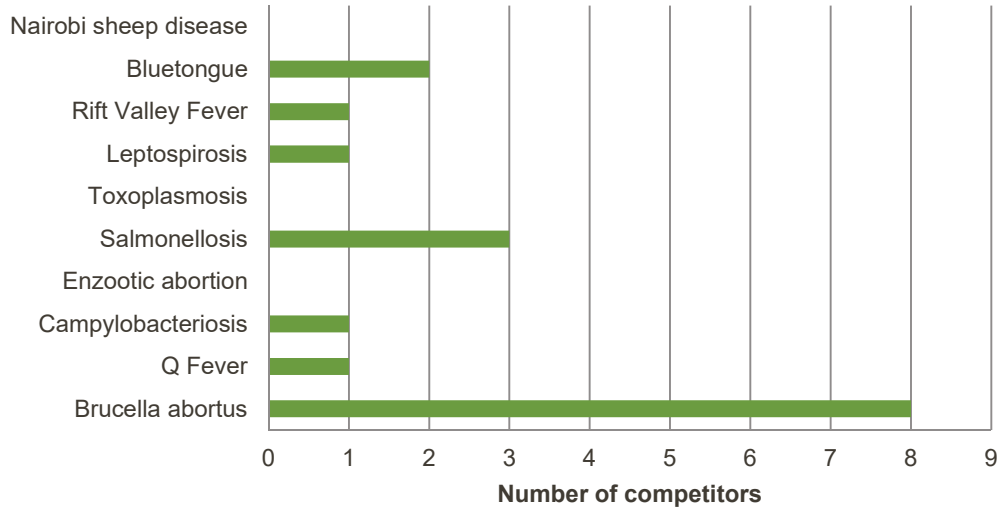
Source: Interviews with or written responses from competitors (n=16) and experts (n=8).

Case comparison disease exercise

To help determine whether the project spurs development and innovation of new technologies, the evaluation will compare the progress towards a *B. melitensis* vaccine with the progress that the competitors make towards similar zoonotic diseases (Exhibit 6-2). If it appears at endline that progress for *B. melitensis* has deviated from trends in R&D in other areas, that will help to determine the degree to which the project incentivised development that would not have otherwise occurred.

As of 2018, competitors were working on 7 of the 10 comparison diseases (Exhibit 6-2). *B. abortus* was the disease most commonly being worked on by competitors (8 of 11). A few competitors were conducting R&D on salmonellosis, bluetongue, rift valley fever, leptospirosis, campylobacteriosis, and Q fever. Nairobi sheep disease, toxoplasmosis, and enzootic abortion were not being researched by the competitors.

Exhibit 6-2. Comparison diseases competitors work on

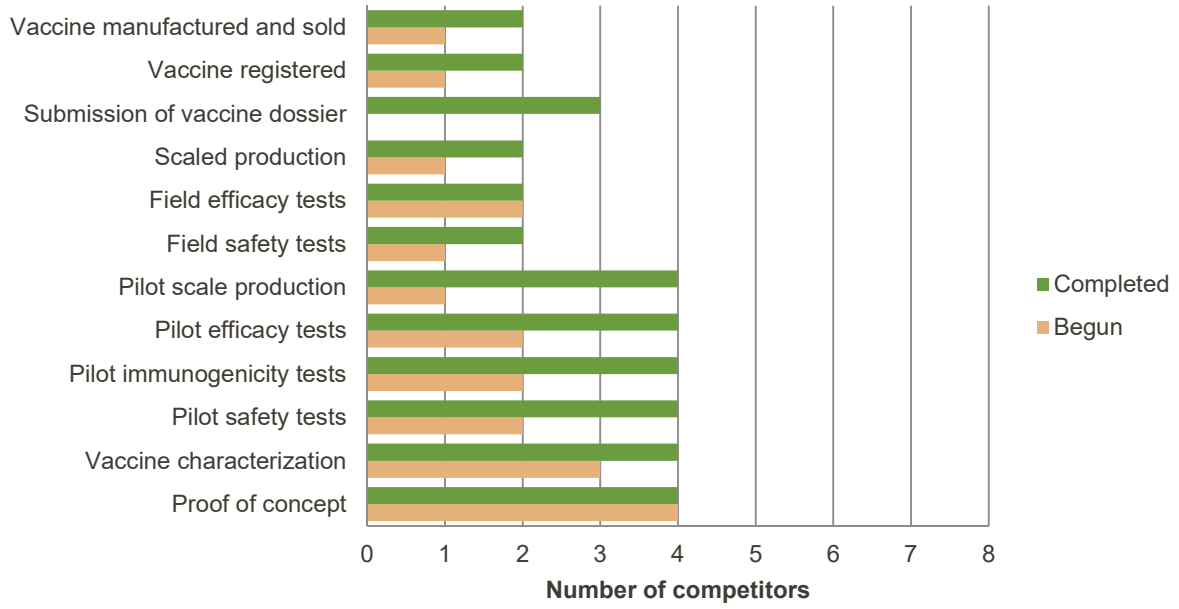


Source: Competitor online survey responses (n=11).

Because *B. abortus* was most commonly worked on, we present more detail on the stages of R&D for *B. abortus* (Exhibit 6-3). Along each step of vaccine development, the steps through pilot scale production were completed by four competitors and field safety and efficacy tests

were completed by two, and two have completed R&D and have manufactured and sold a vaccine (not necessarily sold in developing countries).

Exhibit 6-3. Competitor progress towards a *B. abortus* vaccine



Source: Competitor online survey responses (n=8).

7. Baseline Findings: Development impact

The technology specifications used in the competition were well suited to address key constraints that livestock producers in low- and middle-income countries face, as they comprehensively addressed all limitations of current vaccines. In fact, the experts we interviewed agreed that a vaccine that fulfils only some of the MVP requirements could still make a significant contribution to *B. melitensis* control. Therefore, they expressed a concern that some groups with promising ideas for partially addressing the current vaccine limitations may have decided to forego the competition because of the very high standards they would need to meet to win the prize.

A second issue that all interviewees with knowledge of the international *Brucella* vaccine market raised is that procurement and supply of the vaccine to smallholders is likely to involve public actors (i.e., government animal health departments) and international organisations. This has important implications for companies, as vaccine sales are likely to depend on tenders to support large, coordinated control programs, which can limit their interest to distribute even after a vaccine is developed. This has been until now the main channel to commercialise *B. melitensis* vaccine.

A third concern that experts raised is that the impacts of an improved vaccine may not be realised if vaccination implementation is not improved. A main barrier may be poor vaccination program implementation rather than the vaccine itself.

8. Baseline Findings: Cost-effectiveness

Key Findings

The breakeven analysis shows that the benefit of the project (not counting the human health benefits) will equal its cost if1.2 million sheep or goats are vaccinated with the new vaccine.

This Challenge Project aims to develop a *B. melitensis* vaccine appropriate for developing country contexts, but does not focus on the second stage of encouraging its adoption. Accordingly, the evaluation will not directly assess the project's impact on human or animal health, the project's cost-effectiveness, or the cost per unit of its ultimate impact on the health of animals and humans. Instead, assuming that a new vaccine is developed, the evaluation conducted a prospective breakeven analysis to estimate the number (or percentage) of animal vaccinations at which the costs of the current project will equal its benefits, not counting the human health benefits given the complexity in estimating these benefits. The prospective analysis estimates the human health impacts of the vaccine (measured in the number of DALYs averted) separately for several plausible scenarios of animal vaccination rates.

There are a few reasons why the results of this prospective analysis are only indicative. First, the winning vaccine has yet to be developed, and therefore the analysis is based on *assumptions* about the potential vaccine. Second, scant data are available to estimate the value of the vaccine in preventing infections from *B. melitensis*. For example, a key variable in the analysis is the risk of an unvaccinated animal contracting *B. melitensis*; however, there are few published data on the prevalence of *B. melitensis* in sheep and goats in developing countries. Anecdotal evidence also suggests that these prevalence rates almost certainly vary widely across countries, implying a vide variability in country-specific impacts of delivering a *B. melitensis* vaccine. Therefore, one contribution of this work is to also shed light on the evidence gap that exists in assessing the benefits of the vaccine, with the hope that resources are made available to fill these gaps. Ultimately, despite the uncertainty in the results, this analysis still provides a useful prospective estimation of the potential return on investment in the *B. melitensis* vaccine. Third, the prospective breakeven analysis does not include human health benefits because of the complexity in estimating these benefits for different vaccination rates.

In the prospective analysis, the expected benefits of the vaccine are compared to the budgeted costs of the project, which include all AgResults costs related to the project (e.g., the cost of the prize, project verification, and project management). The next section presents the project costs followed by a discussion of the breakeven analysis that includes the project impacts.

Project costs

The analysis evaluates the project costs from the perspective of the donor organisation; it does not consider other costs incurred by the competitors or other stakeholders, such as the costs to develop, manufacture, or distribute the vaccine. Therefore, the cost-effectiveness study assesses the returns to donors for their investment. Accordingly, the project costs are from the AgResults budget reported to the Steering Committee by the Secretariat. The Secretariat tracks its management costs across all of the projects rather than individually. Therefore the Secretariat management cost for the *B. melitensis* project is an estimate based on discussions with the Secretariat. The total estimated project costs are shown in Exhibit 8-1.

Exhibit 8-1. Budgeted costs of the AgResults Brucellosis Vaccine Challenge Project

Budget item	Cost
Prize	$30,000,000
Prize management	$5,505,000
Project verification	$90,000
Total	**$35,595,000**

Benefits of vaccinating animals

The avoided losses to the value of animals depends on the number of *B. melitensis* infections avoided in animals. The calculations of losses depend on the existing *B. melitensis* prevalence rates. In the absence of these prevalence data, the analysis uses the *B. melitensis* prevalence rate in Rossetti et al. (2017) of 35%. Since this assumption in Rossetti et al. (2017) is arbitrary, we conducted a sensitivity analysis with lower- and upper-bound prevalence estimates, and is discussed further below. The analysis assumes that in all cases *B. melitensis* vaccination would reduce the prevalence to zero.

Following Rossetti et al. (2017), we conducted a simple thought experiment to estimate the impacts of *B. melitensis* on a flock of 100 goats, in which we assumed that 35 goats contract *B. melitensis*, and out of those, 25 pregnant goats abort. The avoided losses to value of each animal are based on the avoided cost of culling the infected animal and replacing it at $50. The culled animals are also assumed to be sold at $20 each.[8] Further, the loss of aborted kids is valued at $30 each. We also assume that costs are incurred for a veterinarian visit and for serological tests. Exhibit 8-2 summarizes the assumptions regarding costs, which are taken from Rossetti et al (2017). The total cost includes the cost for replacement goats, lost value of aborted kids, and veterinary costs, including costs to test the entire flock for *B. melitensis* infection. The costs are partially offset by value of the culled animals that are sold. Therefore, the assumed impact of a *B. melitensis* outbreak on a flock of 100 goats is calculated as A – B + C + D + E = $2,800. This means that the value of losses avoided from vaccinating a flock of 100 goats against an outbreak of *B. melitensis* is $2,800, or $28 per animal vaccinated.[9]

Exhibit 8-2. Vaccination cost assumptions used in breakeven analysis

	Cost assumptions	Cost per animal	Number of animals	Total cost
A	Replacing culled animals	$50	35	$1,750
B	Value from selling culled animals	$20	35	$700
C	Lost value of aborted kids	$30	25	$750
D	Visit from veterinarian	$200	N/A	$200
E	Serological tests	$8	100	$800

[8] Note that in many cases, there may be no value for the culled animals. These animals may simply be destroyed to prevent the further transmission of disease. In this case, the value of the vaccine would increase, given that the impacts from infection with *B. melitensis* would be even more costly to the farmer.

[9] The Rossetti et al. (2017) analysis also included assumptions about the value of milk-producing goats, rather than meat goats. The estimated impact of a *B. melitensis* outbreak on a flock of milk goats ($74,600) was more than 20 times higher than the impact on a flock of meat goats. This analysis uses the value of the impact on meat goats to be conservative.

Breakeven analysis

The breakeven analysis estimates the number of animals that need to be vaccinated for the prospective benefits of the project to equal the prospective costs, where the benefits and costs are described as above.

Main results. Using the value of avoided losses from the Rossetti et al. (2017) analysis of $28 per animal, the breakeven number of animals to be vaccinated that equates the benefits to the cost of the project is 1.2 million sheep or goats.[10] In other words, if the value provided by the winning vaccine is $28 per animal *and* if more than 1.2 million animals are vaccinated, the avoided losses from the value of animals will be greater than the costs incurred by the project, not including the human health benefits. To place it in context, 1.2 million animals represents approximately 0.18% of the sheep and goats in the affected countries. This is estimated based on an identification of countries with incidence of human brucellosis in Pappas et al. (2006).[11] Of the developing countries identified by Pappas, there is a total population of approximately 709 million sheep and goats, according to data from FAO (2018).

Sensitivity analysis. The sensitivity analysis considered lower- and upper-bound values for variables that influence the estimated impacts of *B. melitensis*, and for which the data are uncertain. These variables include *B. melitensis* prevalence, cost of replacing a culled animal, and veterinary costs. These are discussed below.

- *B. melitensis prevalence.* The Rossetti et al. (2017) analysis assumed the prevalence of *B. melitensis* is 35%. A separate analysis of *B. melitensis* in Mongolia assumes a prevalence ranging between 20% and 70% (Roth et al. 2003). On applying the lower- and upper-bound *B. melitensis* prevalence of 20% and 70%, the estimated avoided loss is $20–$46 per animal vaccinated, respectively.
- *Cost of replacing a culled animal.* The Rossetti et al. (2017) analysis assumes the cost of replacing a culled animal is $50. Other published values for sheep and goats range from $31 in Liberia (Miklyaev et al. 2017) to $220 in Mexico (Montiel et al. 2015). Using these replacement costs, the estimated cost of replacing a culled animal ranges from $21 to $88 per animal, respectively.
- *Efficacy of the vaccine.* The Rossetti et al. (2017) analysis implicitly assumes 100% efficacy of the *B. melitensis* vaccine. However, the vaccine is likely to be less than 100% effective. The rules for the project require a minimum efficacy of 80%. If the efficacy were 80%, the average value of the vaccine would be $22 per animal, resulting in a breakeven number of animals of 0.23% of sheep and goats in countries with incidence of *B. melitensis*.
- *Veterinary cost.* The Rossetti et al. (2017) analysis assumes $1,000 in veterinary costs. These costs may vary widely across countries, or they may not be incurred at all in some cases. If the veterinary costs are not incurred, the estimated impacts would be $18 per animal.

Based on the lower- and upper-bound estimates of the key variables, the lower- and upper-bound estimate of avoided losses ranges from $18 to $88 per animal vaccinated. To be conservative, the sensitivity analysis assumed values ranging from $2 to $100 per animal (Exhibit 8-3).

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[10] While the Rossetti et al. (2017) analysis is based on goats, we assume sheep and goats have a similar value.

[11] Pappas et al. does not specify *B. melitensis*, but given that most human brucellosis infections are due to *B. melitensis*, it is assumed that the countries identified in Pappas represent countries with incidence of *B. melitensis.*

Exhibit 8-3. Sensitivity analysis results

Assumed value of vaccine per animal	Breakeven number of animals to be vaccinated	Percentage of sheep and goats in developing countries with B. melitensis infections
$2	17,797,500	2.51%
$5	7,119,000	1.00%
$10	3,559,500	0.50%
$20	1,779,750	0.25%
$28	1,200,000	0.18%
$50	711,900	0.10%
$100	355,950	0.05%

The results of this sensitivity analysis show that as long as the assumed value of the vaccine is greater than $5 per animal, the breakeven number of animals vaccinated is always less than 1% of the sheep and goat population in affected countries. In other words, if at least 1% of these animals are vaccinated, and the vaccine prevents brucellosis in all vaccinated animals, it is likely that the benefits provided by the vaccine will outweigh the costs of the project. While the breakeven number of animals is relatively small compared to the total population of sheep and goats in developing countries with *B. melitensis* infections, it could be a much higher percentage of the sheep and goat populations of individual countries. This is the case without accounting for other benefits of vaccination, which includes the benefits from avoided human health impacts. Insofar as the human health impacts are not included in the breakeven analysis, the breakeven vaccination rate is an underestimate of the benefits of vaccination. The data were not adequate to monetize these benefits (only DALY estimates are available), and there is fair degree of complexity in estimating human health impacts at different vaccination rates. For example, the breakeven analysis discussed above estimates a vaccination rate of less than 1%. It is not possible to meaningfully extrapolate the results of Roth et al. (2003) to such a low vaccination rate.[12] However, the human health impacts and related cost-effectiveness analysis are presented separately below.

Human health impacts and related cost-effectiveness

The breakeven analysis could not include human health impacts because of the complexity of estimating the impacts for any vaccination rate. Instead the evaluation estimated the potential impacts of the vaccine on human health and the potential cost-effectiveness of the project for vaccination rates for which data are available.

B. melitensis infection in humans does not generally result in mortality, but the illness can last for several years. Roth et al. (2003) estimate an average of 3 DALYs per case of *B. melitensis* infection in humans, based on an *ex ante* analysis of a potential 10-year *B. melitensis* vaccination program in Mongolia.[13] Combing this assumption with country-level

[12] If the trend from Roth et al. (2003) were extrapolated linearly to estimate the impacts of a 1% vaccination rate, the resulting impacts on DALYs would be negative. We anticipate the actual effects of a 1% vaccination rate to be small, but positive. However, we lack data to estimate the actual effects of a 1% vaccination rate.

[13] Their analysis assumed animal vaccination rates of 32% (which account for 65% efficacy and 50% coverage) and 52% (which account for 65% efficacy and 80% coverage). We acknowledge that these vaccination rates are quite high, and that the results of Roth et al. (2003) for Mongolia may not be transferrable to other countries. However, additional published information is lacking to evaluate other vaccination rates. Further, the results of Roth et al. (2003) are based on vaccination for both *B. melitensis* and *B. abortus*, but the results do not differentiate between the benefits from vaccinating for the different diseases. This analysis assumes the benefits accrue mostly from avoiding infection from *B. melitensis*.

data on the human *B. melitensis* incidence rates from Pappas et al. (2006), the current number of DALYs in each developing country with incidence of human *B. melitensis* is estimated at approximately 370,000 per year, or 3.7 million over 10 years.[14]

Using these assumptions, we estimate that the winning vaccine could save between 600,000 and 3,000,000 DALYs over 10 years in developing countries with incidence of human *B. melitensis*, if similar vaccination rates could be achieved. The cost-effectiveness of the vaccine is estimated at $59 and $12 per DALY averted, assuming a 32% and 52% vaccination rate, respectively (Exhibit 8-4). Across developing countries, the vaccine would be cost-effective with these vaccination rates, using World Bank guidelines.[15]

Exhibit 8-4. Assumed animal vaccination rate and DALYs averted

	Developing Countries	
	32%	**52%**
Reduction in DALYs over 10 years	600,000	3,000,000
Cost per DALY averted	$59	$12

The limitations of this analysis are driven by the lack of data. First, the analysis relies on the only available average values from the literature on the number of averted DALYs from different vaccination rates, which is based on data for Mongolia. The actual rate of decline in the human infection from *B. melitensis* could differ widely across countries.

Second, human health impacts analysis are highly sensitive to the assumptions about the vaccination rate. The difference between a 32% and a 52% vaccination rate leads to a five-fold difference in the number of DALYs averted and the cost per DALY averted. These are also relatively high global vaccination rates. If the vaccination rates are lower, the cost effectiveness values would be much higher. Similarly, the results are also sensitive to the assumptions about the DALYs per case of *B. melitensis*. If the number of DALYs per case of *B. melitensis* was 1.55, or half as much as the assumption from the base case analysis, then the cost per DALY averted would be twice as much, ranging from $23 to $115 per DALY averted.

[14] Roth et al. assume that the rates of decline in *B. melitensis* infection rates will be 17% and 83%, respectively, over a 10-year period.

[15] World Bank guidelines suggest that public health interventions with a cost per DALY of less than US$283 (2017 dollars) are very cost-effective, although there are also alternate guidelines on cost-effectiveness.

9. Baseline Findings: Sustainability

At this early stage, it is not possible to determine whether the impact of the project will be sustainable. The sustainability of the impact will largely depend on manufacturing and sales of the improved vaccine, the willingness of governments and producers to pay for the vaccine, market stability, and extent of producer adoption. A thorough assessment will need to be conducted when there is greater certainty around these factors.

At the baseline, experts we interviewed indicated that the sustainability of vaccination programs would depend on:

- **Advocacy.** Improving advocacy efforts to educate and raise awareness of the benefits of vaccination with governments and smallholders in countries where brucellosis is endemic, and to foster the support of donors for the regular funding of vaccination.
- **Government commitment and funding.** Improving the regularity of vaccination in affected countries by better integrating vaccination into government annual budgets and disease control plans.
- **Market stability.** Reducing reliance on donor funding, or improving the regularity of donor funding, for vaccination to help stabilise the demand for a vaccine and improve manufacturers' desire to serve the market.
- **Producer adoption.** Improving vaccine availability and advocacy efforts with smallholders to improve their willingness to pay for and adopt the vaccine.

The market for *B. melitensis* vaccine has been irregular and subject to allocation of funds from governments in affected countries or from international donors to brucellosis control. The competitors are tackling some of the issues that preclude uptake of the vaccine and engagement of governments on sustained control efforts. These issues include the trade-off between disease protection and vaccine safety.

10. Baseline Findings: Early learning

The evaluation drew early learnings related to the competition design, including the prize structure, and early implementation of the project, including prize governance. These early learnings may evolve over the course of the project. At this early stage, the opinions the competitors expressed on the rules and adjudication of the competition are in the majority supportive. Nevertheless, the evaluation received some feedback that can inform future R&D competition design around three broad topics—prize size, prize rules, and prize governance (Exhibit 10-1).

Exhibit 10-1. Interviewed respondents' feedback on competition design

Recommendation	Non-commercial competitors	Commercial competitors	Experts	Total
Prize size and timing				
Allow the $1 million milestones to be dispersed earlier, contingent on achieving steps towards the milestones.	1	2	0	3
Increase size of prizes to attract large companies.	0	0	1	1
Increase upfront payment to allow smaller actors to pursue R&D.	1	0	0	1
Prize rules				
Change the requirement for registration in the U.S., EU, Australia, or Japan, since filing in a foreign language will be challenging.	1	0	0	1
Allow registration in China, where there is a high market potential.	1	0	0	1
Relax the requirement for BSL3 facilities if local regulators require only BSL2.	0	1	0	1
Prize governance				
Ensure comparability between competitors by standardizing prize judging criteria (e.g., "protection").	1	1	0	2
Avoid admitting competitors into the competition without awarding a milestone 1 payment.	0	1	0	1
Conduct the judging at the same time for all competitors.	0	1	0	1
Simplify the competition rules.	0	1	0	1

Prize size: Adapting the size of the prize to attract the desired applicants to the competition

A competitor and one expert noted that the milestone payments were too small to attract the largest veterinary health companies. Instead, the competition attracted predominantly academic institutions and small commercial competitors, as was expected by AgResults. One respondent noted that they thought that the prizes need to involve substantially larger payments to attract large industrial actors:

> *"If your grand prize is a hundred million, then I think that then you're getting more people at the table, more companies at the table".*

The evaluation team is aware that the prize was meant to attract smaller, more cost-effective players. However, this strategy also carries a higher degree of risk, insofar as large commercial entities have more experience and resources to move products from concept to

market than less-experienced competitors. The selected applicants may face more challenges than large commercial competitors to achieve good manufacturing practices and to register a new product.

Another risk associated with a small first payment is that some applicants (especially from universities and small companies) may enter the competition to receive the initial $100,000 prize to support their research efforts, without the intent of proceeding to the next phase to develop the vaccine. While this investment may ultimately advance the field of vaccine research, it will be "wasted" from the standpoint of developing a usable product. The evaluation will assess these risks as the competition progresses.

Prize size: Structuring milestone payments to target particular competitor types

There is initial indication that different types of competitors may varyingly respond to the same prize structure. Three commercial competitors and one academic competitor that were not awarded a milestone 1 payment have either terminated their R&D effort or seconded it to a third party. Of the competitors that were awarded a milestone 1 prize, two (one commercial, one academic) reported that the award was of little value either because of the advanced stage of development that their organization had achieved, or because of its relatively small size compared to the overall development cost. One competitor noted that the milestone 1 prize would be more appropriate for applicants at the concept stage of R&D.

Given these findings, for future R&D project design, it is worth assessing the type of competitor that is motivated by an initial milestone payment. For competitors at larger institutions who are in later stages of R&D, the initial milestone payments may be nice to have but non-essential. Future R&D prize competitions could structure the milestone payments to try to attract competitors at different stages of R&D depending on what is desirable for the competition. The prize could use small upfront payments to attract competitors at early stages of R&D or large final prizes to attract competitors at late stages of R&D.

Prize rules: Considering geographical variability when defining rules

Several respondents commented on building flexibility into the registration process citing challenges with filing in foreign languages or given the potential market, for example in China. Others commented on relaxing the BSL3 requirement if country processes allow BSL2 facilities, which is an adaptation that AgResults made to the competition rules in 2018. The broader learning that emerges out of these comments is the need to consider regional variations in policies and context when designing prize competitions that span multiple countries.

Prize governance: Adapting the selection process to improve perception of fairness in the application cycle

Applications were accepted over a period of approximately one year. The judging panel evaluated the applications quarterly, either awarding milestone 1 prizes immediately to successful applicants, or, more frequently, deferring them for later review after requesting clarifications to the applications. This sequential process created a perception amongst some competitors that the earlier applications were more likely to be accepted than the later ones, even though competition information stressed that applications would be accepted on a rolling basis. For example, one competitor stated:

> *"It wasn't until much later in the process that I learned we were being judged and awarded every quarter, because I would have applied much earlier [had I known]".*

The competition data shows that proportionately fewer awards were given in later quarters when there higher numbers of applications reviewed. A simultaneous review schedule could improve the perceived level of fairness of the award process.

Prize governance: Clearer standards for assessing progress

Some competitors raised concerns regarding the standards by which a number of requirements will be assessed, such as demonstration of efficacy or safety of the vaccine candidates. Unless the details of such trials are more precisely defined, it may be possible for some competitors to design their trials in such a way that positive results are more likely to be obtained. Respondents noted that competitors could take advantage of the rules to design tests to yield more positive results, giving them an unfair advantage. AgResults revised the competition rules in April 2018 to specify more clearly the requirements for the milestone 2 award. It is worth continuing to evaluate the rules as the competition progresses to ensure that the judging process and requirements are clear and transparent.

11. Evaluation next steps

The evaluation team will continually monitor the project implementation as part of its ongoing qualitative assessment. We will conduct short, annual, semi-structured interviews or online surveys with competitors on their progress and activities in each year. We will also remain in regular communication with the Project Manager, the Secretariat, DFID, and the Steering Committee to keep track of any issues that arise, their importance to the project implementation, and how they are eventually resolved. This will continue up to the point of the endline.

The evaluation team will conduct the endline once AgResults awards the grand and the best-in-class prizes. If the best-in-class prize is never awarded, we will complete the endline in the final year of the project. Should neither of these prizes ever be awarded, we will continue our ongoing assessment and conduct the endline in the final year of the project.

References

Abt Associates. 2016. AgResults Evaluation Design: Brucellosis Vaccine Pilot. Bethesda, MD: Abt Associates.

AgResults. 2014. Pilot Business Plan: Reducing the Impact of Brucellosis on Smallholder Farmers: Incentivizing Research and Development for an Improved Brucellosis Vaccine. AgResults Secretariat.

———. 2015. Brucellosis Vaccine Development Pilot: Revised Executive Pilot Business Plan. London: AgResults Secretariat.

———. 2018. Steering Committee Meeting Presentation. October, Edinburgh, Scotland. AgResults Secretariat.

Berndt, Ernst, Rachel Glennerster, Michael Kremer, Jean Lee, Ruth Levine, Georg Weizacker, and Heidi Williams. 2007. "Advance market commitments for vaccines against neglected diseases: Estimating costs and effectiveness". *Health Economics* 16: 491-511.

Boudreau, Kevin, Nicola Lacetera, and Karim Lakhani. 2011. "Incentives and problem uncertainty in innovation competition: an empirical analysis". *Management Science* 1-21.

Brunt, Liam, Josh Lerner, and Tom Nicholas. 2008. "Inducement Prizes and Innovation". Discussion Paper. Norwegian School of Economics.

Corbel, M.J. 2006. *Brucellosis in humans and animals.* Geneva: World Health Organization.

Dean, Anna S., Lisa Crump, Helena Greter, Esther Schelling, and Jakob Zinsstag. 2012. "Global Burden of Human Brucellosis: A Systematic Review of Disease Frequency". *PLoS Neglected Tropical Diseases* 6(10): e1865.

FAO (Food and Agriculture Organization of the United Nations). 2018. FAOStat. Rome, Italy. http://www.fao.org/faostat/en/#data

Fisher, William W., and Talha Syed. 2012. "Prizes". In *Infection: The Health Crisis in the Developing World and What We Should Do about It.* Stanford, CA: Stanford University Press.

Iowa State University. 2015. "Vaccines: *B. melitensis".* http://www.cfsph.iastate.edu/Vaccines/disease_list.php?disease=brucella-melitensis&lang=en

Kay, Luciano. 2012. *Technological Innovation and Prize Incentives: The Google Lunar X Prize and Other Aerospace Competitions*. Cheltenham, UK: Edward Elgar.

Kremer, Michael, and Heidi Williams. 2010. "Incentivizing Innovation: Adding to the Tool Kit". In *Innovation Policy and the Economy, Volume 10*, edited by Josh Lerner and Scott Stern, 1-17. Chicago, IL: University of Chicago Press.

Kremer, Michael, and Rachel Glennerster. 2004. *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases*. Princeton, NJ: Princeton University Press.

Mansfield, Edwin. 1984. "R&D and Innovation: Some Empirical Findings". In R&D, Patents, and Productivity, Zvi Griliches, ed., pp. 127-154. Chicago: University of Chicago Press.

Miklyaev, Mikhail, Majid Hashemi, and Melani Schultz. 2017. Cost-Benefit Analysis of Liberia's Rice and Goat Value Chains. No. 2017-01. JDI Executive Programs.

Montiel, David Oseguera, Mieghan Bruce, Klaas Frankena, Henk Udo, Akke van der Zijpp, and Jonathan Rushton. 2015. "Financial analysis of brucellosis control for small-scale goat farming in the Bajío region, Mexico". *Preventive Veterinary Medicine* 118, no. 4: 247-259.

Mueller-Langer, Frank. 2013. "Neglected infectious diseases: Are push and pull incentive mechanisms suitable for promoting drug development research?" *Health Economics, Policy, and Law* Apr 8(2): 185-208.

Murray, Fiona, Scott Stern, Georgina Campell, and Alan MacCormack. 2012. "Grand Innovation Prizes: A theoretical, normative, and empirical evaluation". Research Policy 41: 1779-1792.

Pappas, Georgios, Photini Papadimitriou, Nikolaos Akritidis, Leonidas Christou, and Epameinondas V. Tsianos. 2006. "The new global map of human brucellosis". *The Lancet Infectious Diseases* 6: 91-99.

Roth, Felix, Jakob Zinsstag, Dontor Orkhon, G. Chimed-Ochir, Guy Hutton, Ottorino Cosivi, Guy Carrin, and Joachim Otte. 2003. "Human health benefits from livestock vaccination for brucellosis: case study". *Bulletin of the World Health Organization* 81: 867-876.

Singh, B.B., N.K. Dhand, and J.P.S. Gil. 2015. "Economic losses occurring due to brucellosis in Indian livestock populations". *Preventive Veterinary Medicine* 119(3–4): 211-215.

Spickler, Anna Rovid. 2018. Brucellosis: Brucella melatensis. Retrieved from http://www.cfsph.iastate.edu/DiseaseInfo/factsheets.php.

Verger, Jean-Michel, Maggy Grayon, Etienne Zundel, Patrick Lechopier and Veronique Olivier-Bernardin. 1995. "Comparison of the efficacy of *Brucella suis* strain 2 and *B. melitensis* Rev. 1 live vaccines against a *B. melitensis* experimental infection in pregnant ewes". *Vaccine* 13(2): 191-196.

Vetvac. 2010. http://www.vetvac.org/

WHO (World Health Organization). 2005. "The control of neglected zoonotic diseases. A route to poverty alleviation". Accessed at: http://apps.who.int/iris/bitstream/10665/43485/1/9789241594301_eng.pdf

Williams, Heidi. 2010. "Incentives, prizes, and innovation". Accessed at: http://www.nsf.gov/sbe/sosp/tech/williams.pdf

World Bank and TAFS Forum. 2011. *World Livestock Disease Atlas.* Accessed at: http://www.tafsforum.org/livestock-disease-atlas.html

Yang, X., J. A. Skyberg. L. Cao, B. Clapp, T. Thornburg, and D.W. Pascual. 2013. "Progress in Brucella vaccine development". *Frontiers in Biology* (Beijing) 8 (1): 60-77.

Annex A

Interview guides

Experts and stakeholders

GENERAL

1. Can you tell me a little about your role?

2. In which countries/regions do you work? Is vaccination of small ruminants against *B. melitensis* practiced in these areas? If so, to what degree?

3. Is *B. melitensis* vaccination part of a government-led program? What other activities and programs address Brucellosis control in small ruminants?

4. Where is *melitensis* vaccine currently used? What are the regions where this disease is endemic, but vaccine is not used?

***B. MELITENSIS* VACCINE R&D**

5. Can you describe the current market for *B. melitensis* vaccine in small ruminants?
    a. Who are the main buyers for the *B. melitensis* vaccine? Where are they located?
    b. How attractive is the market relative to other livestock vaccines?
    c. Have there been any changes in the market in recent years?

6. What is the future market potential in annual sales for existing *B. melitensis* vaccine for small ruminants?

7. How would the market change if an improved vaccine became available?

8. What size global market (dollars in annual sales) is needed to attract vaccine manufacturers to develop vaccines for this disease?

9. What challenges do companies face developing *B. melitensis* vaccine?

10. What could prompt companies to increase or decrease investment in *B. melitensis* vaccine development?

11. Who are the main players in *B. melitensis* vaccine R&D globally/in your region?

12. Who are the main players in *B. melitensis* vaccine manufacturing globally/in your region?

13. What are the strengths and weaknesses of the current *B. melitensis* vaccines?

14. Have there been any significant scientific advances in in recent years that would allow a new *B. melitensis* vaccine to be brought to market?

15. What improvements in the *B. melitensis* vaccines do you see on the horizon?

SMALLHOLDER LIVESTOCK PRODUCER CONSTRAINTS TO *B. MELITENSIS* VACCINATION

16. How knowledgeable are smallholder livestock producers about *B. melitensis*? How risky do they see *B. melitensis*?

17. What are the key constraints faced by smallholder livestock producers that limit vaccination for *B. melitensis*?

18. What would help increase the rate of vaccination for *B. melitensis* among smallholder livestock producers?

19. Would the advances in *B. melitensis* vaccines that you spoke about make them more suitable for use by smallholder livestock producers?

20. What price per vaccine do you think smallholder livestock producers in developing countries/your region would be willing to pay for a *B. melitensis* vaccine for small ruminants?

21. What changes to livestock vaccine supply chains or distribution would be needed to make *B. melitensis* vaccines more accessible to smallholder livestock producers?

BRUCELLOSIS VACCINE COMPETITION

22. How attractive are the results-based financial incentives (such is used in AgResults competition) to vaccine developers?
    a. How large should the financial incentive be to result in changes in private sector investment?

23. How feasible do you think these milestones are within the next 5 years?

FINAL QUESTIONS

24. Is there anything else you would like to tell us that we have not already discussed?

25. Do you have suggestions for other organizations or individuals we should speak to in order to learn more about these topics?

26. Can we contact you in the future if we have more questions?

27. Do you have any questions for us about the evaluation?

Competitors – Non-commercial

RESPONDENT BACKGROUND

1. Can you tell me a little about your research group and your role?

STATE OF *B. MELITENSIS* VACCINE R&D

2. What are the strengths and weaknesses of the current Rev-1 *B. melitensis* vaccine?

3. What vaccine needs of livestock producers in countries where *B. melitensis* is endemic are currently not met?

4. What do you consider to be key recent advances that will help further the development of a *B. melitensis* vaccine?

B. MELITENSIS VACCINE R&D AT COMPETITOR ORGANIZATION

5. Does your group work on other livestock vaccines? What is the priority of *B. melitensis* vaccine research relative to other livestock R&D for your research group?

6. What is the history of your research group's work on the development of *B. melitensis* vaccine? When and why did you become involved in this research? What are your long-term objectives?

7. What do you see as the major obstacles to the development of a *B. melitensis* vaccine by your group?

8. Has your research group partnered with industry in the past for *B. melitensis* or other animal health vaccine work? If yes, please describe.

9. For the AgResults competition, how and when do you plan to find an industry partner? What role do you anticipate the industry partner playing in *B. melitensis* vaccine development?

VACCINE MARKET AND SALES

10. How familiar are you with the current state of the market for *B. melitensis* vaccine sales in small ruminants? If familiar, can you describe it?

11. Have you developed other livestock vaccines which are now in the marketplace? Does your research group or university earn money from the sale of these vaccines?

12. What constraints, if any, might you face in registering a *B. melitensis* vaccine?

VACCINE PRIZE COMPETITION

About the application process

13. How and when did you learn about the AgResults Brucellosis vaccine prize?

14. Why did you decide to enter the competition? Who was involved in the decision to enter?

15. Approximately how many person-hours did it take you/your research group to develop an application?

16. What is your level of satisfaction with the judging process? Was it fair? Was the feedback you received from the judges useful?

17. What is your level of satisfaction with the clarity of competition rules?

18. What are the advantages and limitations of milestone prizes over upfront payments? Would you prefer smaller upfront payments to larger milestone prize?

19. What would you change about the competition?

About your team

20. Did you have a dedicated team working on the *B. melitensis* vaccine development prior to competition? If yes, did you have to change this team for the competition? In what way?

21. Can you describe how many full time equivalents are working on this project? What is their area of expertise?

22. Are there additional partners, capabilities, or resources which you think your research group might need, and which you do not currently have, to achieve the competition specifications?

23. Do you think the minimum viable product requirements and best in class requirements are achievable for your current team within the competition timeframe?

24. What, if any, effect has participation in the AgResults vaccine competition had on your research group's *B. melitensis* vaccine work so far? Has this competition produced any effect on the development of other livestock vaccines or on other components of your research program?

25. Are there any important players in *B. melitensis* vaccine R&D which were not selected into the competition?

26. [If appropriate] How will/did your organization/research group use the first milestone prize?

CONCLUDING

27. Is there anything else you would like to share with us that we have not discussed already?

28. Was there anyone else who plays an important role in the competition in your organization or research group who we should interview?

29. Do you have any questions for us about the evaluation?

30. We have a few more questions which are easier to answer in an online survey. Would you be willing to complete it? It should take 5-10 minutes.

Competitors – Commercial

RESPONDENT BACKGROUND

1. Can you tell me a little about your role in the organization?

STATE OF *B. MELITENSIS* VACCINE R&D

2. What are the strengths and weaknesses of the current Rev-1 *B. melitensis* vaccine?

3. What vaccine needs of livestock producers in countries where *B. melitensis* is endemic are currently not met?

4. What do you consider to be key recent advances that will help further the development of a *B. melitensis* vaccine?

B. MELITENSIS VACCINE R&D AT COMPETITOR ORGANIZATION

5. What factors do you consider when deciding whether to invest in vaccine development for livestock? What is the process for making these decisions and who is involved?

6. What is the priority of *B. melitensis* R&D relative to other livestock R&D for your company?

7. What is the history of your organization work on the development of *B. melitensis* vaccine? When and why did you become involved in this R&D?

8. What are your long-term research and commercial objectives?

9. What are the major obstacles to the development of a *B. melitensis* vaccine at your organization?

VACCINE MARKET

10. Are you currently selling Rev-1 vaccine? What are the main types of buyers for your company? What types of organizations are your main competitors for Rev-1 vaccine?

11. What are your primary concerns about the *B. melitensis* vaccine market?

12. Have there been changes to the market in recent years? Do you anticipate changes in the next 5 years?

13. Can you describe the market potential for your company for a *B. melitensis* vaccine for small ruminants, in terms of types of buyers, volume of sales, and purchasing countries?

14. What return on investment does your company need to generate from sales of a *B. melitensis* vaccine to be considered profitable?

15. What constraints, if any, might you face in registering a *B. melitensis* vaccine?

VACCINE PRIZE COMPETITION

About the application process

16. How and when did you learn about the AgResults Brucellosis vaccine prize?

17. Why did your organization decide to enter the competition? Who in your organization was involved in the decision to enter?

18. Approximately how many person-hours did it take your organization to develop an application?

19. What is your level of satisfaction with the judging process? Was it fair? Was the feedback you received from the judges useful?

20. What is your level of satisfaction with the clarity of competition rules?

21. What are the advantages and limitations of milestone prizes over upfront payments? Would you prefer smaller upfront payments to larger milestone prize?

22. What would you change about the competition?

About your team

23. Did you have a dedicated team working on the *B. melitensis* vaccine development prior to competition? If yes, did you have to change this team for the competition? In what way?

24. Can you describe how many full time equivalents are working on this project? What is their area of expertise?

25. Are there additional partners, capabilities, or resources which you think your research group might need, and which you do not currently have, to achieve the competition specifications?

26. Do you think the minimum viable product requirements and best in class requirements are achievable for your current team within the competition timeframe?

27. What, if any, effect has participation in the AgResults vaccine competition had on your organization's *B. melitensis* vaccine R&D so far? Has this competition produced any effect on the development of other livestock vaccines or on other components of your research and development program?

28. Are there any important players in *B. melitensis* vaccine R&D which were not selected?

29. [If relevant] How will/did your organization use the first milestone prize?

CONCLUDING

30. Is there anything else you would like to share with us that we have not discussed already?

31. Was there anyone else who plays an important role in the competition in your organization or research group who we should interview?

32. Do you have any questions for us about the evaluation?

33. We have a few more questions which are easier to answer in an online survey. Would you be willing to complete it? It should take 5-10 minutes.

Online questionnaire

Note, this questionnaire was programmed in SurveyGizmo, an online survey platform, so the administered questionnaire had an interactive format.

1. Please enter the annual expenditures in United States Dollars (USD) by your company or research group on <u>all</u> animal vaccine research and development.

   2016: _____ USD

   2017: _____ USD

2018 planned: _____ USD

2. Approximately, what percentage of the total animal vaccine research and development expenditures at your company/research group was for *Brucella melitensis* vaccine?

   2016: pull-down menu: <10%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%

   2017: pull-down menu: <10%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%

   2018 pull-down menu: <10%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%

3. Approximately how many full time staff work on *Brucella melitensis* vaccine research and development at your company/research group on an annual basis?

   2016: pull-down menu: 0, 1-2, 3-5, 6-10, 11-20, >20, >50

   2017: pull-down menu: 0, 1-2, 3-5, 6-10, 11-20, >20, >50

   2018 planned: pull-down menu: 0, 1-2, 3-5, 6-10, 11-20, >20, >50

4. Please indicate all stages of *Brucella melitensis* vaccine development reached and completed by your company/research group as of December 2017. Select all that apply.

Stage	Begun	Completed
Proof of concept → A and B	❑	❑
Vaccine characterization → A and B	❑	❑
Pilot safety tests in target animal → A and B	❑	❑
Pilot immunogenicity tests in target animal → A and B	❑	❑
Pilot efficacy tests in target animal → A and B	❑	❑
Pilot scale production → A and B	❑	❑
Field safety tests → A and B	❑	❑
Field efficacy tests → A and B	❑	❑
Scaled production → A and B	❑	❑
Submission of vaccine dossier → 5	❑	❑
Vaccine registered → 5	❑	❑
Vaccine manufactured and sold → 5	❑	❑
Other. Please describe: _____	❑	❑

   A. Have you started manufacturing for *B. melitensis* vaccine production? Select one.
      - ❑ Yes, through a partner
      - ❑ Yes, without a partner
      - ❑ No, but are currently developing a plan with a partner
      - ❑ No, but are currently developing a plan without a partner
      - ❑ No, not yet developed a plan

   B. Do you have a plan for *B. melitensis* vaccine registration? Select one.
      - ❑ Yes
      - ❑ No, but are currently developing a plan
      - ❑ No, not yet developed a plan

5. On a scale of 1-5, where 1=not at all likely and 5=very likely, please indicate your level of confidence that your team can achieve these *B. melitensis* vaccine elements within the Competition timeframe:

   Minimal Viable Product Elements

MVP elements	Enter number 1-5 1=not at all likely 5=very likely
In all stages of gestation, no more than 5% of the vaccinated animals should abort due to the vaccine strain	
Shedding levels similar or less than for Rev-1 in milk, aborted material, and vaginal and semen secretions	
Any adverse reactions are compliant with applicable regulatory criteria	
Long-term persistence of the vaccine strain for whole *Brucella* bacterium attenuated vaccines is less than 2 months	
Minimum age of vaccination 3 months	
If a live organism, demonstrates no reversion to virulence	
Administration via ocular (palpebral), other mucosal, intramuscular, subcutaneous, or other suitable innovative route	
The vaccine demonstrates 80% or higher protection compared with among unvaccinated animals in controlled trial conditions	
Single vaccination annually, or duration of protection lasts for at least two gestations with a single vaccination.	
Shelf life no less than 18 months under controlled conditions	
Affordable for smallholder farmers, including a sufficiently low cost of manufacturing.	

Best-in-class elements

Best-in-class elements	Enter number 1-5 1=not at all likely 5=very likely
A multi-species vaccine with cross protection against both *B. melitensis* in small ruminants and *B. abortus* in cattle	
An efficacious vaccine meeting the MVP requirements that would offer an enhanced level of human and animal safety	
Vaccine stays effective after being kept at a minimum of 45 degrees centigrade for 3 weeks or more	
Facilitates clearing of the infection and/or reduces abortions or clinical signs of infection in animals	

6. Does your company/research group currently work on vaccines for any of the following diseases? Select all that apply.
   - ❑ Brucellosis caused by *Brucella abortus*
   - ❑ Q Fever
   - ❑ Campylobacteriosis
   - ❑ Enzootic abortion
   - ❑ Salmonellosis
   - ❑ Toxoplasmosis
   - ❑ Leptospirosis
   - ❑ Rift Valley Fever
   - ❑ Bluetongue
   - ❑ Nairobi sheep disease
   - ❑ My organization does not work on vaccines for any of these diseases → Skip 7

7. Please indicate the stage of development for [preload disease from 5] vaccine reached by your company/research group.
    - ❑ Vaccine characterization
    - ❑ Pilot safety tests in target animal
    - ❑ Pilot immunogenicity tests in target animal
    - ❑ Pilot efficacy tests in target animal
    - ❑ Pilot scale production
    - ❑ Field safety tests
    - ❑ Field efficacy tests
    - ❑ Scaled production
    - ❑ Submission of vaccine dossier
    - ❑ Vaccine registered
    - ❑ Vaccine manufactured and sold

8. Please feel free to add information or make comments related to the Brucellosis vaccine competition.

    _____

Annex B

Exhibit B-1. Current Rev-1 vaccine manufacturers

Country	Rev-1 vaccine manufacturer
Egypt	Veterinary Serum and Vaccine Research Institute
France	*Ceva Santé Animale*
India	Indian Immunologicals Ltd.
Iran	Razi Vaccine & Serum Research Institute
Jordan	Jordan Bio-Industries Center (JOVAC)
Mexico	*National Biologicos Producer Veterinarios*
Spain	*CZ Veterinaria* S.A.
	Laboratorios SYVA S.A.
South Africa	Onderstepoort Biological Products Ltd.
Turkey	ATA FEN Inc.
	Dollvet
	Vetal Company

Source: Vetvac (2010); Iowa State Center for Food Security and Public Health (2018).

Exhibit B-2. Select public sector actors involved in R&D on *Brucella* vaccines (ordered by country)

Institution type	Institution
R&D institutes	Harbin Veterinary Research Institute (China)
	Institute of Chemical Technology (Mumbai) (India)
Government research institutions	*Instituto Nacional de Tecnología Agraria* (Argentina)
	Instituto de Sanidad Ganadera (Argentina)
	Animal and Plant Health Agency (UK)
	Institute of Animal Health and Veterinary Biologicals (India)
	Volcani Center (Israel)
	National Veterinary Research Institution (Nigeria)
	Walter Reed National Military Medical Center (USA)
	National Animal Disease Center (U.S. Department of Agriculture) (USA)
Government-owned veterinary vaccine manufacturers	*Empresa Colombiana de Productos Veterinarios* S.A. (Colombia)
Government-owned Rev-1 vaccine manufacturers	Veterinary Serum and Vaccine Research Institute (Egypt)
	Razi Vaccine & Serum Research Institute (Iran)
	National Biologicos Producer Veterinarios (Mexico)
Universities	University San Martin (Argentina)
	Universidade Federal de Minas Gerais (Brazil)
	University of Alberta (Canada)
	Agricultural University of China (China)
	Huazhong Agricultural University (China)
	Universidad Autónoma (Mexico)
	Universidad de Navarra (Spain)

Institution type	Institution
	London School of Hygiene and Tropical Medicine (UK)
	Jawaharlal Nehru University (USA)
	Montana State University (USA)
	Virginia Tech University (USA)
	Purdue University (USA)
	University of Florida (USA)
	Texas A&M University (USA)

Source: AgResults (2014).

Exhibit B-3. Select private sector actors involved in R&D on *Brucella* vaccines (ordered by country)

Institution Type	Institution
Biotech companies	IVAC Bio (South Africa)
	Brucella Green Vac (Spain)
	Disease Treatment Technologies (USA)
Veterinary vaccine producers	Virbac (France)
	Hester (India)
	Colorado Serum Company (USA)
Commercial Rev-1 producers	*Ceva Santé Animale* (France)
	Indian Immunologicals Ltd. (India)
	Jordan Bio-Industries Center (Jordan)
	CZ *Veterinaria* S.A. (Spain)
	Laboratorios SYVA S.A. (Spain)
	Onderstepoort Biological Products Ltd. (South Africa)
	ATA FEN Inc. (Turkey)
	Dollvet (Turkey)
	Vetal Company (Turkey)

Source: AgResults (2014).

Annex C

Exhibit C-1. Comparison of the MVP requirements with the existing Rev-1 vaccine characteristics (as of 2015)

Element		AgResults MVP requirements	Rev-1
Species/animal		*B. melitensis* in goats or sheep	*B. melitensis* in goats and sheep
Animal safety	Safety in pregnant animals	In all stages of gestation, no more than 5% of the vaccinated animals should abort due to the vaccine strain.	20% of the vaccinated animals abort due to the vaccine strain.
	Shedding	On par with or less than Rev-1 in milk, aborted material, and vaginal and semen secretions	Shedding occurs in milk and reproductive tract.
	Adverse reactions	Any adverse reactions should be compliant with applicable regulatory criteria and must be deemed acceptable by the judging panel.	No/minimal adverse reactions
	Long-term persistence of the vaccine strain/ colonisation	For whole *Brucella* bacterium attenuated vaccines, persistence should be less than two months.	Long-term persistence of the vaccine strain/ colonisation occurs.
	Minimum age for vaccination	Three months	-
	If a live organism	Demonstrates no reversion to virulence.	Reverts to virulence.
Route of administration		Administration via ocular (palpebral), other mucosal, intramuscular, subcutaneous, or other suitable innovative route.	Intravenous or ocular
Efficacy* in pregnant sheep or goats against a *B. melitensis* challenge such that:		The vaccine demonstrates 80% or higher protection** compared with unvaccinated animals in controlled trial conditions; in these trials the challenge dose should be stringent enough that at least 90% of unvaccinated challenged animals abort.	~85% efficacious
Duration of protection		Single vaccination annually, or duration of protection lasts for at least two gestations with a single vaccination.	Productive life of animals
Shelf life		No less than 18 months under controlled conditions.	-
Cost		Affordability for smallholder farmers, including a sufficiently low cost of manufacturing.	Varies

Source: AgResults (2015).
*For efficacy, the data obtained for the vaccine candidate under evaluation may be compared with data for Rev-1 as published in the scientific literature. For example: Verger et al. (1995).
**For all trial results, animals are considered to be protected when no abortion, no excretion of the challenge strain, and no infection at slaughter (in carcasses) occurs.

Exhibit C-2. Best-in-class requirements

Element	AgResults best-in-class requirements
Cross-species protection	A multi-species vaccine with cross-protection against both *B. melitensis* in small ruminants and *B. abortus* in cattle.*
Providing maximum human and animal safety	An efficacious vaccine meeting MVP requirements and offering an enhanced level of human and animal safety by demonstrating that the vaccine strain would no longer be able to replicate, or would have reduced pathogenic potential. This could be accomplished by inactivated, a sub-unit, recombinant, deoxyribonucleic acid (DNA), non-replicating, vectored, or similar vaccine approaches.

Element	AgResults best-in-class requirements
Thermoresistant formulation	Stays effective after being kept at a minimum of 45 degrees centigrade for three weeks or more.
Curative effect on infected animals	Boosts or redirects the immune response to facilitate clearing of infection and/or reducing abortions or clinical signs in these animals at a statistically significant level.

*Product performance for *B. abortus* in cattle should be on par with currently available commercial vaccines.