Protocol for a systematic review of the development and application of the direct mycobacterial growth inhibition assay (MGIA)

1.0 ADMINISTRATIVE INFORMATION

Registry: PROSPERO

Registration number:

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Author contributions: EH will run the searches. HP and RT will independently review search results to assess eligibility; HMcS will be consulted to resolve discrepancies. HP will collect data from eligible papers and with RT will synthesise findings. RT and HP will write the manuscript. HF and HMcS will critically review the manuscript.

2.0 INTRODUCTION

Rationale: The direct mycobacterial growth inhibition assay (MGIA) was first described by Wallis et al. in 2001 for the assessment of TB drugs. Over the past 13 years, we have led efforts to adapt the direct MGIA for the assessment of TB vaccines including optimisation, harmonisation and validation of BCG vaccine-induced responses as a benchmark, as well as assay transfer to institutes worldwide. The direct MGIA has since been applied across species for the evaluation of novel prophylactic and therapeutic TB vaccine candidates, the study of clinical cohorts including those with comorbidities, and to further understanding of potential immune correlates of protection from TB.

Objectives: The aim of this systematic review is to provide a comprehensive update on the development and applications of the direct MGIA since its conception, and to critically evaluate current findings and evidence supporting its utility, highlighting future directions.

3.0 METHODS

Eligibility criteria: i) published up to 15/05/2023; ii) published in a peer-reviewed journal since 2001 (date of first report of the direct MGIA); iii) published in English; and iv) consisting wholly or partially of primary data or discussion of the direct MGIA (defined as a co-culture of a blood or cell sample with mycobacteria followed by quantification using the BACTEC MGIT system) as applied to any species.

Information sources: PubMed, Embase and Scopus

Search strategy: Example search strategy for PubMed:

((((((((((("Biological Assay"[Mesh:NoExp]) OR "In Vitro Techniques"[Mesh:NoExp]) OR "Culture Techniques"[Mesh:NoExp]) OR "Cell Culture Techniques"[Mesh:NoExp]) OR "Primary Cell Culture"[Mesh:NoExp]) OR "Lung"[Mesh:NoExp]) OR "Humans"[Mesh]) OR "Mice"[Mesh:NoExp]) OR "Macaca"[Mesh:NoExp]) OR "Cattle"[Mesh:NoExp]) OR (assay*[Title/Abstract] OR "in vitro"[Title/Abstract] OR "ex vivo"[Title/Abstract] OR "whole blood"[Title/Abstract] OR PBMC*[Title/Abstract] OR "peripheral blood mononuclear cells"[Title/Abstract] OR splenocyte*[Title/Abstract] OR lung*[Title/Abstract] OR pulmonary[Title/Abstract] OR human*[Title/Abstract] OR patient*[Title/Abstract] OR subject*[Title/Abstract] OR participant*[Title/Abstract] OR case[Title/Abstract] OR cases[Title/Abstract] OR mouse[Title/Abstract] OR mice[Title/Abstract] OR murine[Title/Abstract] OR "non-human primate*"[Title/Abstract] OR "nonhuman primate*"[Title/Abstract] OR NHP*[Title/Abstract] OR cattle[Title/Abstract] OR bovine[Title/Abstract] OR cow*[Title/Abstract])) AND ("growth inhibition"[Text Word] OR "mycobacterial immunity"[Text Word] OR "antimycobacterial immunity"[Text Word] OR MGIA[Text Word] OR bactericid*[Text Word] OR "inhibiting growth"[Text Word] OR "anti-mycobacterial immunity"[Text Word])) AND ((("Mycobacterium"[Mesh]) OR "Tuberculosis"[Mesh]) OR (mycobacterial[Title/Abstract] OR mycobacteria[Title/Abstract] OR mycobacterium[Title/Abstract] OR tuberculosis[Title/Abstract] OR BCG[Title/Abstract] OR TB[Title/Abstract])) Filters: English, from 2001 – 2023

Data management: Search results will be imported into Rayyan for screening. Eligible studies will be imported into EndNote Web.

Selection process: HP and RT will independently review search results to assess eligibility in three rounds of screening: titles, abstracts and full-text publications. Discrepancies will be resolved by discussion and consultation with HMcS.

Data collection process: Data collection will be performed independently by HP by manual extraction from methods and results sections of eligible papers, and recorded using Microsoft Excel.

Data items: Data will be collected from eligible papers, where available, on: i) study groups being analysed using the direct MGIA (species, cohorts, sample sizes, interventions); ii) direct MGIA methods (sample type, cell input/volume, mycobacterial inoculum type and quantity, co-culture volume and time period, replicates, controls); and iii) other immune parameters measured.

Outcomes and prioritisation: The primary outcome of interest will be the ability to control mycobacterial growth in the direct MGIA and whether this differs between the study groups under investigation. The secondary outcome of interest will be associations between mycobacterial growth inhibition and specific immune parameters (where measured).

Risk of bias in individual studies: Quality of individual studies will be considered in terms of i) sample size; ii) inclusion of appropriate control groups; iii) use of appropriate assay co-culture conditions or optimisation thereof; and iv) potential confounding factors. Consideration of these factors will be included in the synthesis and discussion of individual study findings.

Data synthesis: Data will be qualitatively synthesised and organised by application (ie. study of drugs, vaccines or clinical cohorts); and within application by species (or cohort in the case of clinical cohorts). Data pertaining to immune correlates from all studies will be synthesised separately and organised by immune parameter. Similarities and differences in direct MGIA outcomes between studies comparing similar groups will be discussed.

Meta-biases: Risk of meta-biases will be reduced by predefining eligibility criteria, using broad and inclusive search terms, searching three independent databases, two authors independently screening search returns, and additional citation screening used to identify missed eligible papers. The ROBIS tool will be applied by an independent colleague to formally assess risk of bias.

Confidence in cumulative evidence: This review does not aim to estimate an effect size. However, the five GRADE domains will be used to structure a discussion around the cumulative evidence that the direct MGIA can provide a biologically relevant read-out and limitations.