FOGARTY

Writing an Implementation Science Manuscript

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From New Haven to Tbilisi: Bacteriophage Discovery & Therapeutics

Professor Felix D'Herelle
Institut Pasteur, 1911-1921
Yale University, 1928-1934
Tbilisi Institute, 1934-1936

Professor George Eliava,
Institut Pasteur, 1918-1921
Founder, Tbilisi Institute,
1923-

Eliava Institute, Tbilisi

A seminal manuscript

Bacteriophage 1:1, 3-5; January/February 2011; © 2011 Landes Bioscience

On an invisible microbe antagonistic to dysentery bacilli. Note by M. F. d'Herelle, presented by M. Roux. Comptes Rendus Academie des Sciences 1917; 165:373–5

I isolated from stools of different individuals convalescent from bacillary dysentery, and also in one a one case from urine, an invisible microbe with antagonistic properties against the Shiga bacillus. It is particularly easy to find in cases of banal enteritis consecutive to dysentery: in convalescents without this complication, the disappearance of the anti microbe follows closely that of the pathogenic bacillus. Despite numerous attempts, I never found (similar) antagonistic microbes, neither in stools from the acute phase nor in stools from normal individuals.

The isolation of the anti-Shiga microbe is simple: a tube with (nutrient) broth is seeded with four to five drops of (liquid) stool, placed into an incubator at 37° and then filtered through a Chamberland L3 candle. A small quantity of an active filtrate, either a broth culture of Shiga bacilli or an emulsion of these bacilli in broth or even physiological saline, causes this culture to arrest its development, the death of the bacilli and then their lysis, which is complete after a time interval varying from a few hours to a few days according to the more or less great amount of the culture and the quantity of added filtrate.

The invisible microbe multiplies in the lysed Shiga culture since a trace of this fluid, if transferred into a new Shiga culture, me intensity: I have made till today over 50 successive transfers of the first isolated strain. Moreover, the following experiment gives visible proof that the antagonistic activity is produced by a living germ: if one adds a diluted (sample) of a previously lysed culture to a Shiga culture, so that the Shiga culture contains approximately one millionth (of the sample), and if immediately after this, one spreads a droplet of this (Shiga) culture on an agar slant, one obtains after incubation a layer of dysentery bacilli with a certain number of holes ("circles") of about 1 mm in diameter without culture; these points can only represent colonies of the antagonistic microbe: no chemical substance would be able to concentrate on (such) precise points. In working with measured quantities, I have been able to see that a lysed Shiga culture contains five to six billions of filterable germs per cubic centimeter. When introduced into a broth tube, a three-billionth of a cubic centimeter of the Shiga culture above, thus a single germ, suppresses the Shiga culture even after heavy inoculation; the same quantity (of lysate), when added to 10 cm³ of a Shiga culture, sterilizes and lyses it within five or days.

The different strains of the anti microbe which I have isolated, were first active against the Shiga bacillus; by culture in symbiosis with Hiss or Flexner type dysentery bacilli, I was able, after a few passages, to make them antagonistic to these bacilli. I have had no results with other microbes: typhoid and paratyphid bacilli, staphylococci, a.s.o. The appearance of an antagonistic action against Flexner or Hiss bacilli is accompanied by reduced activity against the Shiga bacillus. However, this ability reappears with equal intensity after several cultures in symbiosis; the specificity of the antagonistic action is therefore not inherent to the very nature of the invisible microbe, but is acquired within the organism of the patient by symbiotic culture with the pathogenic bacillus.

In the absence of dysentery bacilli, the anti-microbe does not multiply in any medium, it does not attack dysentery bacilli killed by heat; by contrast, it multiplies perfectly in an emulsion of washed bacilli in physiological saline; it results from these facts that the antidysenteric microbe is an obligate bacteriophage.

The anti-Shiga microbe has no pathogenic effect on experimental animals. The Shiga cultures lysed under the action of the invisible microbe are in fact cultures of the anti microbe and able to protect ("immunize") rabbits against a dosis of Shiga bacilli that kills control animals in five days.

I investigated whether one can detect an anti microbe in typhoid fever convalescents: in two cases, I succeeded to isolate, once from urine and once from stool, a filterable microbe with clear lytic action against the paratyphoid A bacillus, but (it was) less marked than of the anti-Shiga microbe. This action has weakened in subsequent cultures.

In summary, I found in certain dysenteria convalescents that the disappearance of the dysenteric bacillus coincides with the appearance of an invisible microbe with antagonistic properties against the pathogenic bacillus. This microbe, a true immunity microbe, is an obligate bacteriophage; it is a strictly specific parasite, but, if it is limited to one species at a given moment, it can act later on different germs by habituation. It seems thus that in bacillary dysentery, besides an analogous antitonic immunity which derives directly from the organism of the patient, there exists a heterologous immunity caused by an antagonistic microorganism. It is probable that this phenomenon is not specific to dysentery, but is of a more general order since I could make similar observations in two cases of paratyphoid fever.

Translated by Hans-W. Ackermann

DOI: 10.4161/bact.1.1.14941

D'Herelle, F. and Eliava, G. (1921) 'Sur le serum anti-bacteriophage' Compt Rend Soc Biol 84:719.

Today's talk

- Prepare to Write
- Understand the structure & function of each manuscript section
- Reflect on writing strategies for successful publication
- Questions
- Practical exercise with STaRI Reporting Guidelines for IS papers

Before you start your project

- Literature Review
- A prospective study protocol
- IRB approval
  - Journals may require documentation
- Pre-register trials & reviews
  - clinicaltrials.gov
  - International Clinical Trials Registry Platform
  - PROSPERO

Before you start writing

- Pick & rank 2-3 target journals
- Review article types, word limits, & any other journal requirements
- Negotiate author list & position

Overview

- Order for journal review / publication
  - Title Page
  - Abstract / Research-in-Context
  - Manuscript Text
  - References
  - Funding & Acknowledgments (F&A)
  - Figures & Tables
  - Supplementary Materials

- Draft in this order
  1. Title Page / References / F&A
  2. Methods
  3. Figures & Tables / Supplement
  4. Results
  5. Discussion / Conclusions
  6. Introduction
  7. Abstract

References

- Use a Reference Manager
  - EndNote ($$)
  - Zotero ($)
  - Mendeley (Free)
- Format in journal style
- Review for accuracy
  - Corrections in Reference Manager…

Supplementary Materials

- Online Supplement
  - Methods
  - Results
  - Figures & Tables S1, S2, etc
- Data repository
  - datadryad.org
- Analysis Code
  - Github

Title Page

- Review title style from journal
- Reporting guidelines
  - Name study design
  - Avoid specificity
    - (e.g. country name)
- Use MeSH to choose keywords
- Format as an article from the start!

Funding / Acknowledgments

- Many helped you get here – say thanks
  - Funders (in a separate section)
  - "Study participants" (not by name)
  - Institutions & policymakers
  - Administrative staff
- Journals may require written permission of those acknowledged

Methods

- Always start by drafting Methods – you have already done this

- Using a reporting checklist as an outline*
  - **STROBE:** Strengthening the Reporting of Observational Studies in Epidemiology
  - **StaRI:** Standards for Reporting Implementation Studies of Complex Interventions
  - **COREQ:** Consolidated Criteria for Reporting Qualitative Research

- Review word limits & published examples from target journal

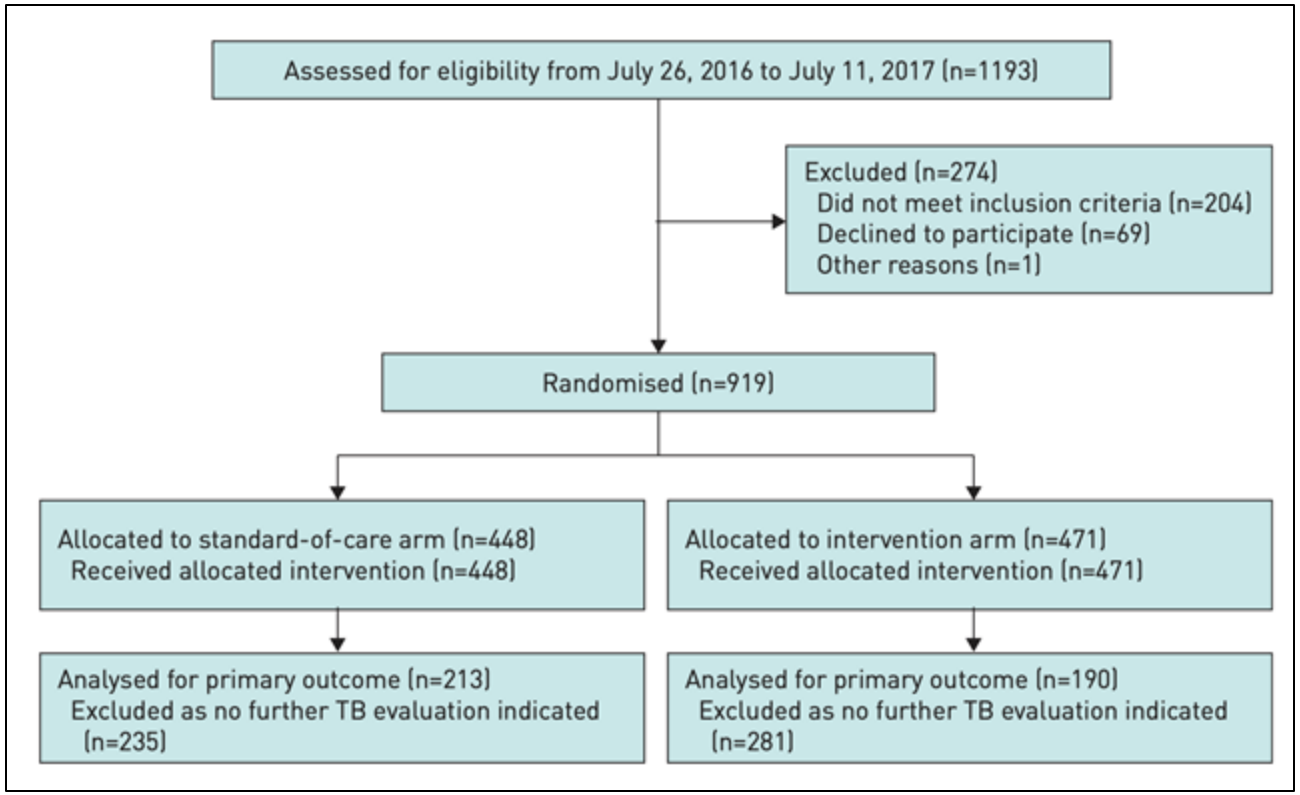
- Avoid presenting results here

*www.equatornetwork.org

Figures & Tables

- Start with Figure 1, *Participant Flow Diagram*
- Then Table 1, *Participant Characteristics*
- Then key results in Figures or Tables (Combined limit 5-6 in total)
  - If table can be summarized in 1-2 sentences, no need for a table
- Unless required to place in-line, place each on its own page after text
- Triple-check findings in Figures & Tables agree with Abstract & Results

Results



- Study timeline & population
  - Figure 1 & Table 1
- Main findings
- Adjusted & sensitivity analyses
- Avoid describing methods here
- Triple-check that findings agree with Abstract, Figures & Tables

Discussion / Conclusions

- What did you find?
  - *Avoid repeating results*
  - *Summarize & highlight significance*
- What gap does research fill?
  - *Focused, comparative literature review*
- Strengths and limitations
  - *Focus on methodology over content*
- Recommendations - Be specific!
  - *For policymakers*
  - *For researchers*

Introduction

- Significance of the health condition
- Evidence-based practice & gap
- What is known in the literature
- What is unknown
- Study objective

Abstract

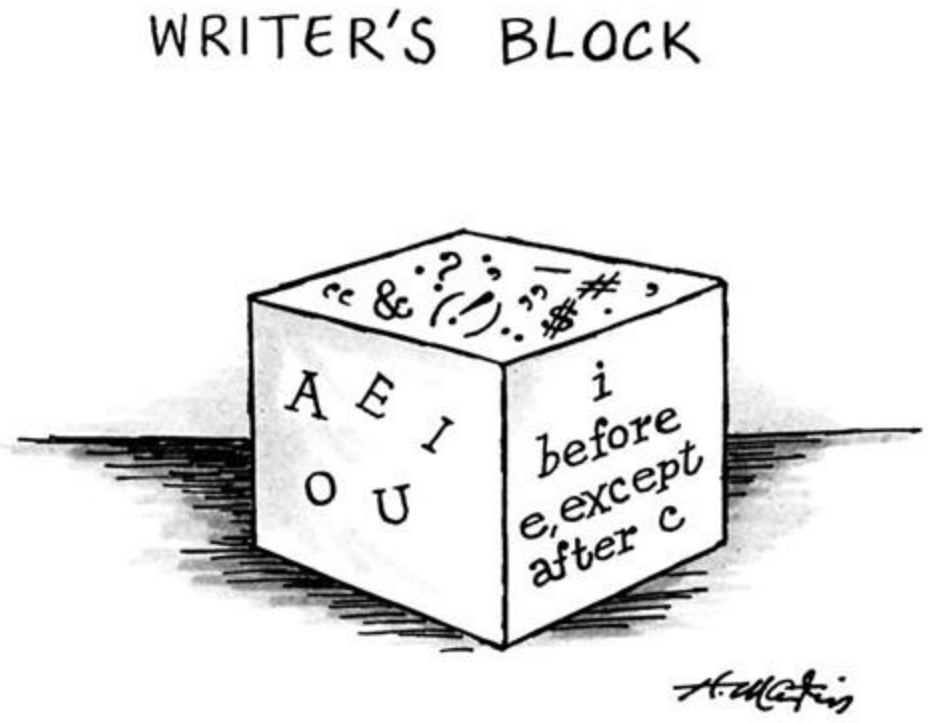
- Journal guidelines
  - Abstract word limits
  - Structured or unstructured?
- Limit Background & Methods
- Emphasize Results & Conclusions
- Triple-check findings agree with Results & Figures & Tables

Research in Context

- Evidence before the study
  - *Summarize intro/literature review*
- Added value of the study
  - *Summarize significance*
- Implications of available evidence
  - *Summarize conclusions*

Finding time to write

- No one strategy fits all
- Every writer gets writer's block
- Onset of flow state not predictable
- Maximize chances through good habits!
- Strategies
  - Set a daily habit of writing
  - Find a setting that suits you on that day
  - Find a writing buddy



Review

- Follow journal guidelines carefully
  - Formatting
  - Expected response timeline
- Track progress online
  - With Journal Staff (Formatting)
  - With Editor (Scientific merit/priority)
  - Out for Review
  - Awaiting Decision
- Set reminders to follow-up regularly
  - Polite inquiry if failing to progress

Wensing et al. Implementation Science (2021) 16:103
https://doi.org/10.1186/s13012-021-01175-3

Implementation Science

EDITORIAL Open Access

Implementation Science and *Implementation Science Communications*: a refreshed description of the journals' scope and expectations

Michel Wensing[1*], Anne Sales[2,3], Paul Wilson[4,5], Rebecca Armstrong[6], Roman Kislov[5,7,8], Nicole M. Rankin[9], Rohit Ramaswamy[10] and Dong (Roman) Xu[11]

Abstract

This editorial provides a comprehensive consolidated overview of the scope and expectations of *Implementation Science* and *Implementation Science Communications*. We remain most interested in rigorous empirical studies of the implementation of evidence-based healthcare practices (including interventions, technologies, and policies) and the de-implementation of practices that are demonstrated to be of low or no benefit. Implementation strategies (e.g., continuing professional education, organizational changes, and financial incentives to enhance the uptake of evidence-based practices) are of central interest to the journals. We see the field as large and complex, with a wide literature that is published in many venues. We urge people for whom it is new to spend some time reading the existing literature, and learning the scope of the work that has already been done, and published, in our journals and in an increasing number of other journals in the field.

Response to Review

- Respond graciously & substantively
  - Acknowledge critiques
  - Make changes to manuscript
  - Quote changes in response letter
  - Include page # / line # (final step)
- Only limited counter to critiques
  - Beyond scope or available data
  - Respectfully w/ strong justification & subject to editor's review
- On time or request extension early

Questions?

STaRI-Based Small Group Activity

Implementation Science Manuscript Writing Workshop

Group Themes for STaRI Checklist (27 Items)

- Group 1 – Why Did We Do This Study? (Items 1–4)
- Group 2 – What Was Implemented and How? (Items 5–10)
- Group 3 – Who, Where, and with What Support? (Items 11–16)
- Group 4 – What Happened? (Items 17–22)
- Group 5 – What Does It Mean? (Items 23–27)

- Each group will:
  - Review their assigned STaRI items
  - Discuss common reporting pitfalls
  - Prepare 1 insight and 1 reporting tip to share back with everyone

STaRI Debrief & Key Takeaways

- STaRI supports full transparency and reproducibility in IS reporting.
- Common pitfalls to watch for:
  - Vague or absent implementation strategy details
  - No reporting of adaptations or unintended effects
  - Outcomes disconnected from process findings
  - No attention to sustainability or equity
- Takeaway: Use STaRI as a planning tool as well as a reporting checklist.
- Good writing will contribute rigorous and usable science for decision-makers.