SD4H Scientific Writing Course
October 31- November 4, 2022

Rigor & Reproducibility

Hong-Ha M. Truong

Friday 4 November 2022

UCSF
University of California
San Francisco
advancing health worldwide™

Rigor & Reproducibility

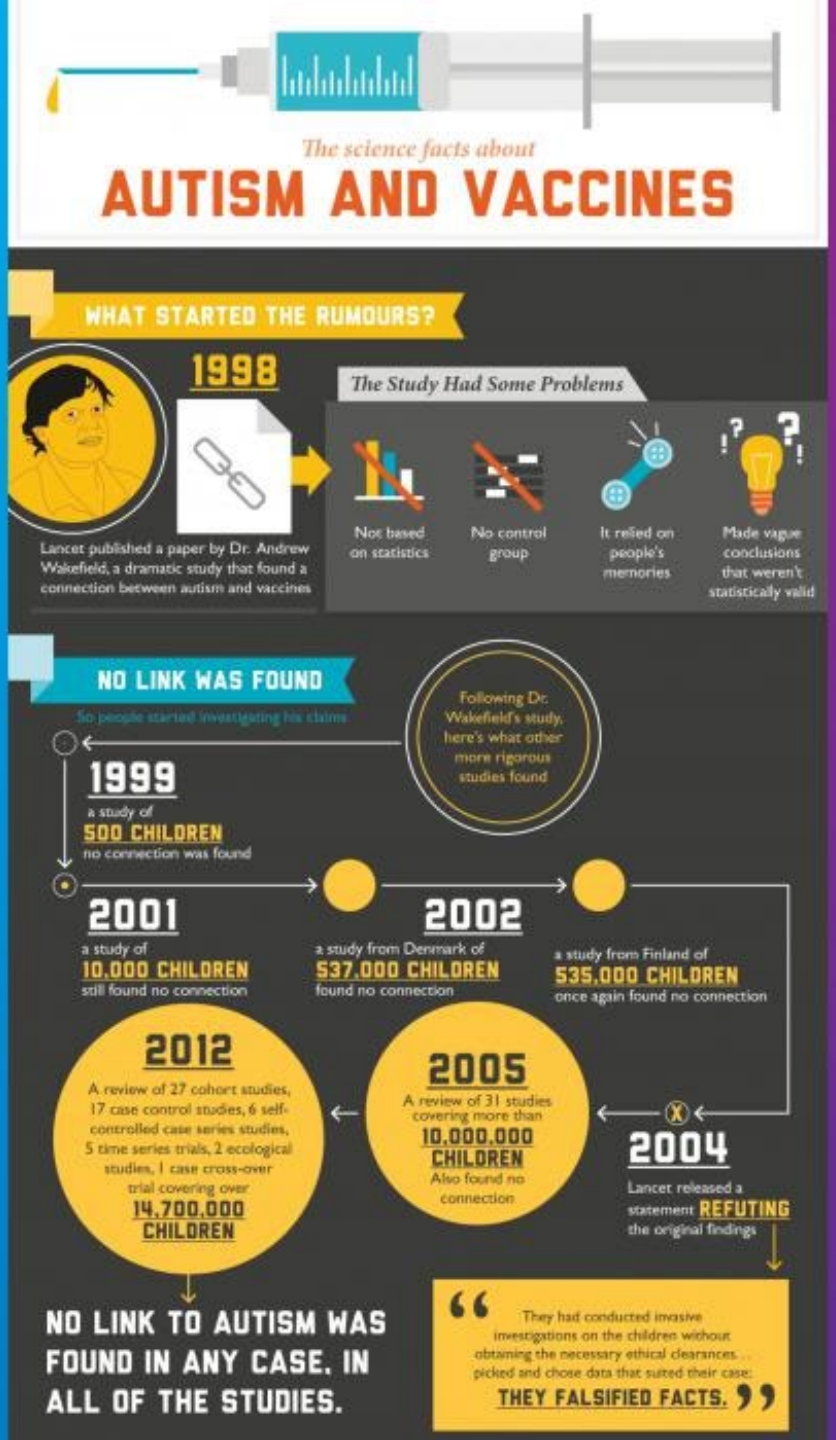
- Cornerstones of science advancement
  - Rigor in designing and performing scientific research
  - Ability to reproduce biomedical research findings
- Scientific rigor is the strict application of the scientific method to ensure unbiased and well-controlled experimental design, methodology, analysis, interpretation and reporting of results
- Reproducibility of a result by multiple scientists validates the original results and readiness to progress to the next phase of research

https://www.nih.gov/research-training/rigor-reproducibility

Why is Rigor & Reproducibility Important?

- Growing awareness in recent years of need for rigorously designed published preclinical studies to ensure they can be reproduced
- Human clinical trials are developed based on preclinical studies that demonstrate a particular effect or outcome
- Dissemination by wider media of scientific findings published in journals or available through preprints sometimes lack important context and leads to spread of misinformation

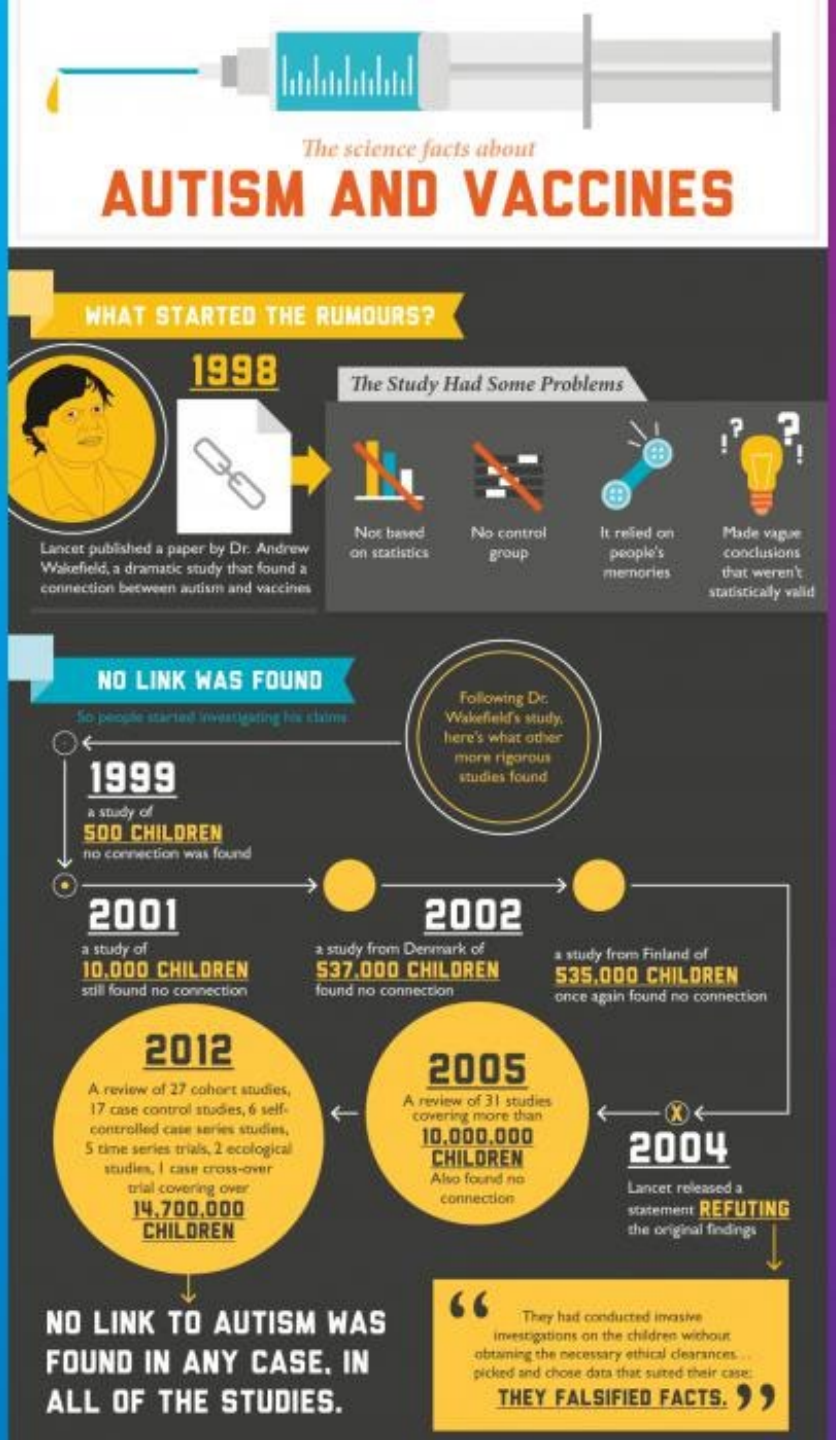
https://www.nih.gov/research-training/rigor-reproducibility



Study in published in The Lancet claimed measles-mumps-rubella (MMR) vaccine increased risk of developing autism

- 12 children with behavioral and intestinal conditions
- 8 children received MMR vaccine

Results could not be replicated by many other studies



Ten authors on original Lancet paper issued a retraction (Mar 2004)

Lancet Editor (Mar 2004)

- "We wish to make it clear that in this paper no causal link was established between MMR vaccine and autism as the data were insufficient."

UK General Medical Council ruled lead author acted "dishonestly and irresponsibly", showing "callous disregard" for the suffering of children involved (Jan 2010)

THE LANCET

Early Report

RETRACTED: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

Dr AJ Wakefield, FRCS, SH Murch, MB, A Anthony, MB, J Linnell, PhD, DM Casson, MRCP, M Malik, MRCP, M Berelowitz, FRCPsych, AP Dhillon, MRCPath, MA Thomson, FRCP, P Harvey, FRCP, A Valentine, FRCR, SE Davies, MRCPath, JA Walker-Smith, FRCP

RETRACTED

DOI: http://dx.doi.org/10.1016/S0140-6736(97)11096-0

Feb 2010

Long-Lasting Impact

- Led to changes in manuscript review process at The Lancet and other journals
  - Increased scrutiny of manuscripts with potential to cause “public health harm”
- Paper still embraced by anti-vaccination groups
  - Promotion of of vaccine misinformation
  - Propagation of vaccine hesitancy
    - Routine vaccinations for childhood diseases
      - Measles, polio
    - Emergent infectious diseases
      - COVID-19

Enhancing Reproducibility in NIH Applications

- NIH is committed to promoting rigorous and transparent research in all areas of science supported by grant programs
- Grant application instructions and review criteria include components that address reproducibility, rigor and transparency
- Four areas of focus
  - Rigor of the prior research
  - Scientific rigor (design)
  - Biological variables
  - Authentication

https://grants.nih.gov/policy/reproducibility/guidance.htm

Rigor of the Prior Research

- Carefully assess the key supporting data for a proposed project to identify weaknesses or gaps in the line of research
- Describe the strength and weaknesses
- Describe plans to address weaknesses
- Describe how experimental design and methods will achieve robust and unbiased results
- Address in research strategy significance and approach sections

https://grants.nih.gov/grants/Rigor-and-Reproducibility-Chart-508.pdf

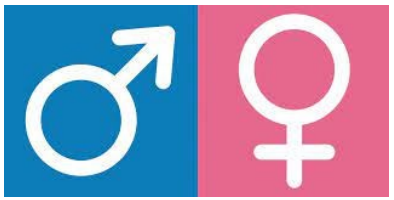
Scientific Rigor (Design)

- Emphasize how proposed experimental design and methods will achieve robust and unbiased results
- Address in research strategy approach section

https://grants.nih.gov/grants/Rigor-and-Reproducibility-Chart-508.pdf

Biological Variables

- Sex, age, weight and underlying health conditions are critical factors affecting health and disease

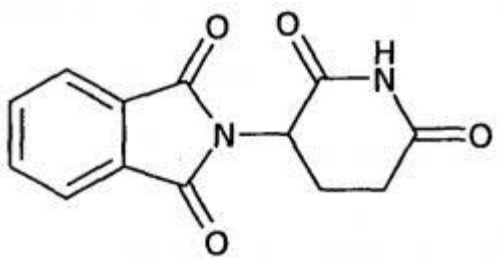


- Sex, in particular, is frequently ignored in animal study designs and analyses
  - Leads to incomplete understanding of potential sex-based differences in basic biological function, disease processes and treatment response

https://grants.nih.gov/grants/Rigor-and-Reproducibility-Chart-508.pdf

Thalidomide

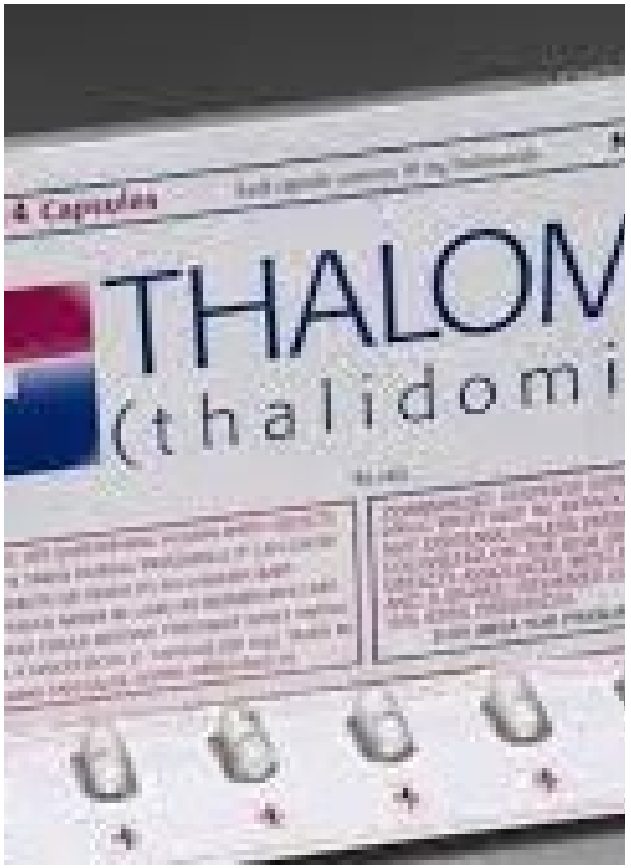
- Developed in the 1950s by Chemie Grünenthal GmbH in West Germany
- Intended as a sedative but soon used to treat wide range of other conditions, e.g., colds, flu, nausea, morning sickness
- Considered to be harmless to humans because during early testing, researchers found it nearly impossible to give test animals a lethal dose
- Licensed in July 1956 in Germany as an over-the-counter drug



Thalidomide

Thalidomide Marketing and Distribution

- US Food & Drug Administration (FDA) did not grant approval
  - Distributing company did not provide clinical evidence to refute reports of patients developing nerve damage in limbs after long-term use
- Drug testing did not involve pregnant women
- Medications during pregnancy not strictly controlled at the time
  - Not known that drug effect could be passed through the placental barrier and harm the fetus



Effects of Thalidomide on Fetal Development

- Association between thalidomide and fetal development first made public in 1961 through letter in The Lancet
- Researchers/doctors slow to make connection
  - Wide range of changes to fetal development
  - Limb deformities similar to other genetic conditions
  - Occurred only if taken 20-37 days after conception
- Thalidomide formally withdrawn in Nov 1961 by Chemie Grünenthal in Germany and worldwide by 1962

Effects of Thalidomide on Fetal Development

- Estimated >10,000 babies affected worldwide
  - Birth defects: limbs, eyesight, hearing, internal organs (brain, heart, kidney, gastrointestinal tract)
  - 40% mortality
  - Increased reports of miscarriages

Impact on Drug Approval Process

- Thalidomide tragedy led to worldwide changes in how drugs are marketed, tested and approved
- Demonstrated for first time species differences in drug reaction/response
  - Mice were less sensitive to thalidomide than other species, e.g., non-human primates, rabbits
- Drug screening policies changed to incorporate several species and *in vitro* tests
- Drugs intended for human use could no longer be approved based solely on animal testing
- Clinical trials for drugs marketed to pregnant women had to prove they were safe for use during pregnancy

Biological Variables

- Sex, age, weight and underlying health conditions are critical factors affecting health and disease
- Sex, in particular, is frequently ignored in animal study designs and analyses
  - Leads to incomplete understanding of potential sex-based differences in basic biological function, disease processes and treatment response
- Explain how relevant biological variables are factored into research designs, analyses and reporting in vertebrate animal and human studies
- Provide strong justification from scientific literature, preliminary data or other relevant considerations when proposing to study only one sex
- Address in research strategy approach section

https://grants.nih.gov/grants/Rigor-and-Reproducibility-Chart-508.pdf

Authentication

- Key biological and/or chemical resources
  - Cell lines, specialty chemicals, antibodies, other biologics
- Briefly describe methods to ensure identity and validity of key resources used in proposed studies
  - May or may not have been generated with NIH funds
  - May differ from laboratory to laboratory or over time
  - May have qualities and/or qualifications that could influence research data
  - Are integral to the proposed research

https://grants.nih.gov/grants/Rigor-and-Reproducibility-Chart-508.pdf

Cell-Line Authentication

- Immortalized or continuous cell lines essential tools in basic and biomedical pre-clinical research
- Model systems for research
  - Molecular origins of human disease
  - Drug discovery and development
- Need to verify identity of cells used in research
  - Derived from correct species and donor
  - Contamination-free
- Skipping authentication could result in lost time, wasted money and withdrawn publications
- International Cell Line Authentication Committee
  - Register of Misidentified Cell Lines
  - 576 cell lines misidentified (June 2021)

https://iclac.org/databases/cross-contaminations/

Authentication

- Key biological and/or chemical resources
  - Cell lines, specialty chemicals, antibodies, other biologics
- Briefly describe methods to ensure identity and validity of key resources used in proposed studies
  - May or may not have been generated with NIH funds
  - May differ from laboratory to laboratory or over time
  - May have qualities and/or qualifications that could influence research data
  - Are integral to the proposed research
- State authentication plan for key resources needed for research, including frequency
  - Do not include authentication data in plan
- Include as an attachment (one page or less)

https://grants.nih.gov/grants/Rigor-and-Reproducibility-Chart-508.pdf