Outlining a Framework for Antimicrobial-Resistance Surveillance Studies

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COMMENTARY

Infection Prevention and Comparative Effectiveness Research

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HEALTH CARE–ACQUIRED INFECTIONS, PARTICULARLY those due to antimicrobial-resistant bacteria, have received significant attention in recent years. Despite work focused on elucidating the epidemiology and effects of such infections, success in curbing their emergence remains elusive. Few new classes of antibiotics are even

example, MRSA screening programs test patients for MRSA carriage and isolate colonized patients to prevent transmission of MRSA. These screening programs indirectly benefit patients who are not isolated. To assess population-level interventions, alternatives to RCTs are needed.

The cluster randomized trial is well suited to study the comparative effectiveness of population-level interventions.[2] Cluster randomized trials may involve randomization at different levels including the full hospital or indi-

JAMA, April 13, 2011—Vol 305, No. 14

Comparative Effectiveness Research

- "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition... CER (aims) to assist…policy makers in making informed decisions that will improve health care at both the individual and population levels"

*Institute of Medicine. 2009. Initial National Priorities for CER, National Academy Press

Patient vs Population-level CER

- Typically, patient who receives treatment directly benefits (choose RCT)
  - Aspirin and myocardial infarction
  - Antimicrobial-coated CVC and catheter-related BSI
- For transmissible pathogens, “others” benefit
  - Screening and isolating MRSA+
  - Antibiotic stewardship programs

Study Designs for Population-level Interventions

- **Quasi-experimental study designs**
  - **Establishing a trial network**
- Mathematical models to simulate interventions
- Cluster-randomized trials

Grimes DA and Schulz KF. Lancet 2992; 539:57-61

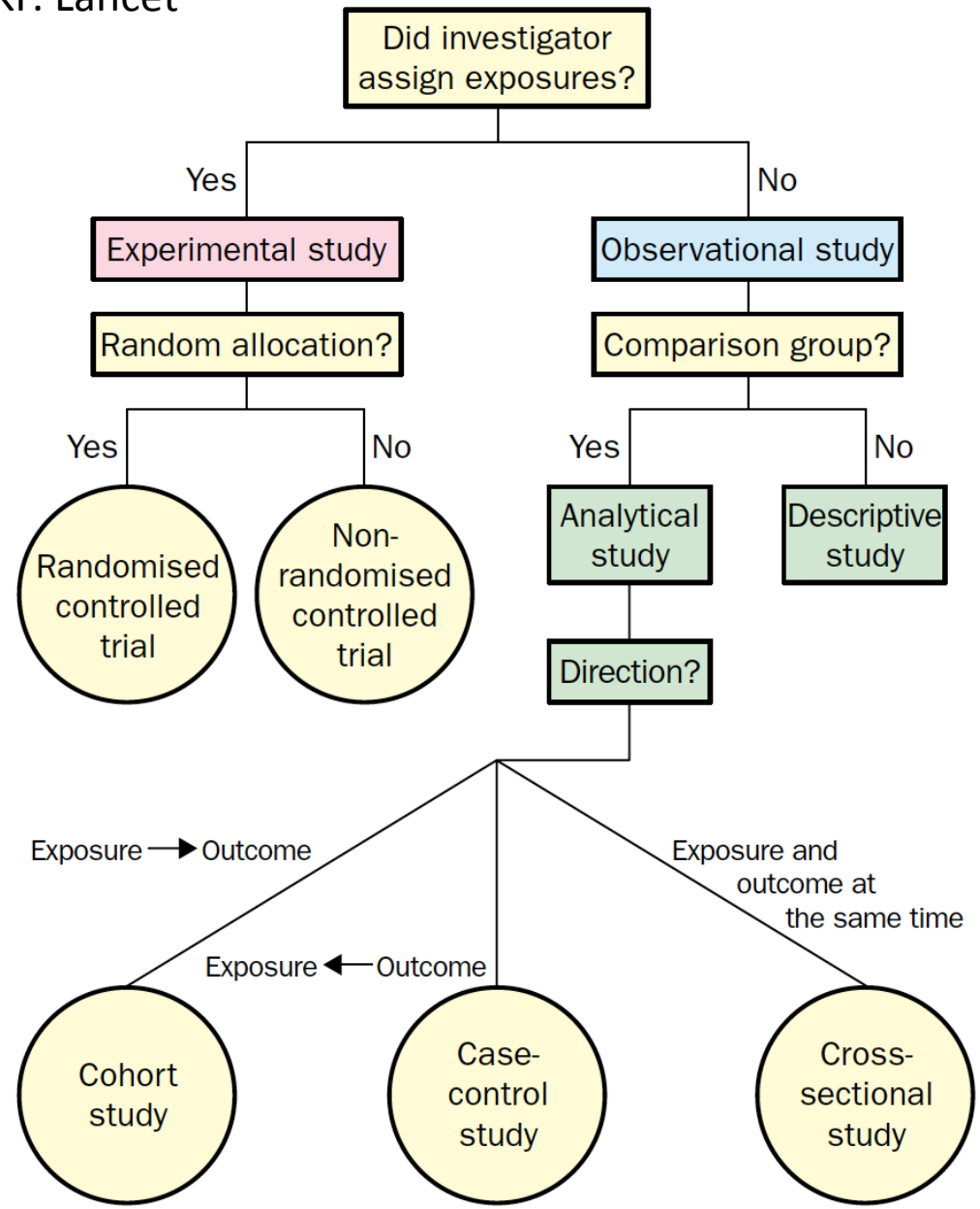


Figure 1: **Algorithm for classification of types of clinical research**

Grimes DA and Schulz KF. Lancet 2992; 539:57-61

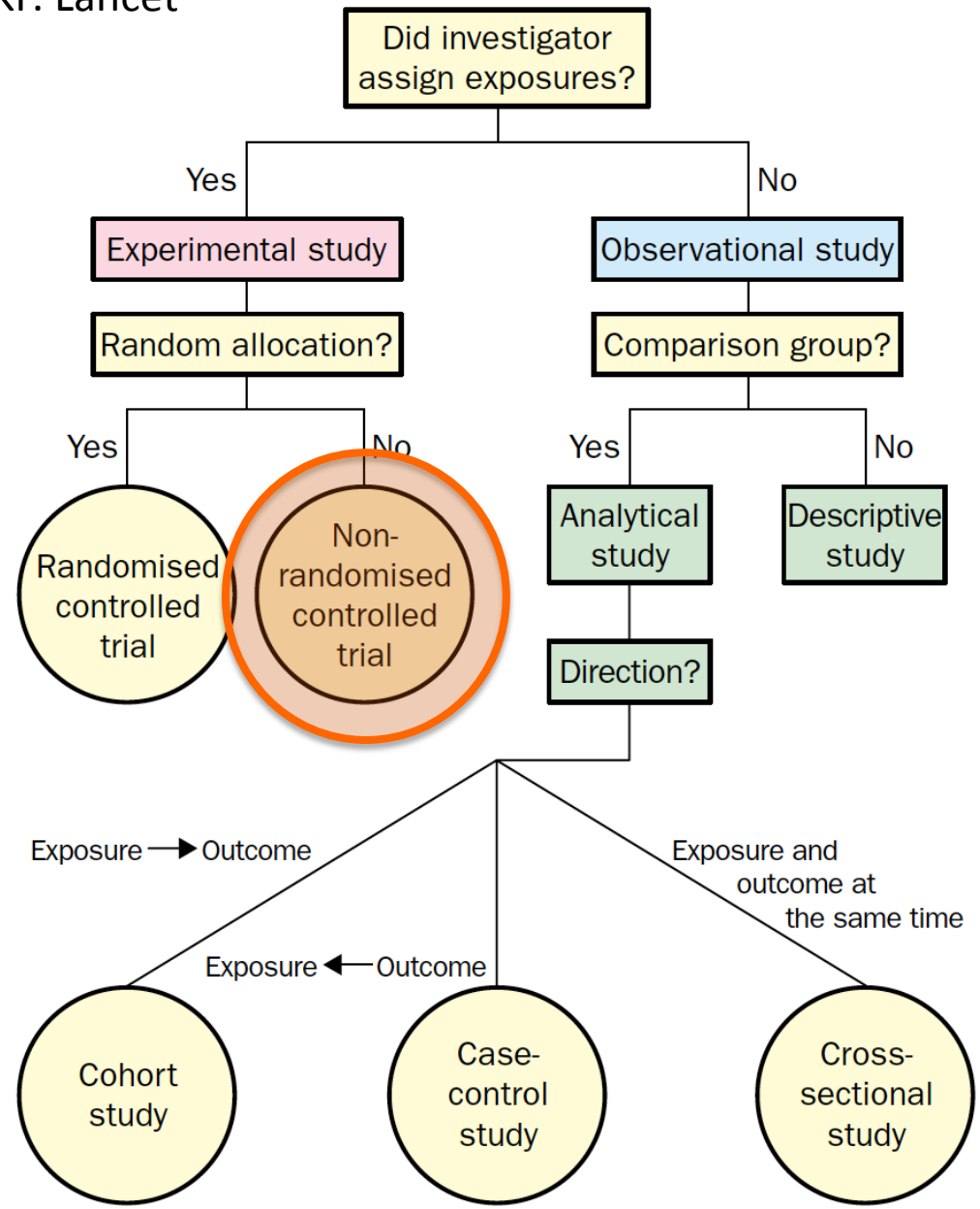


Figure 1: **Algorithm for classification of types of clinical research**

The Quasi-Experiment

- Chosen when RCT or cluster-RCT are not possible (time and money)
- QE data: time-series data (monthly infection rates) BEFORE and AFTER a non-randomized intervention
- $Obs1_{(Before)}$ -----$X_{(intervention)}$----$Obs2_{(After)}$

QE Example

- Intervention: MRSA surveillance and isolation
- Outcome: MRSA bacteremia rates (monthly)

- Measure infection rates BEFORE and AFTER intervention in MICU (or Hospital A)

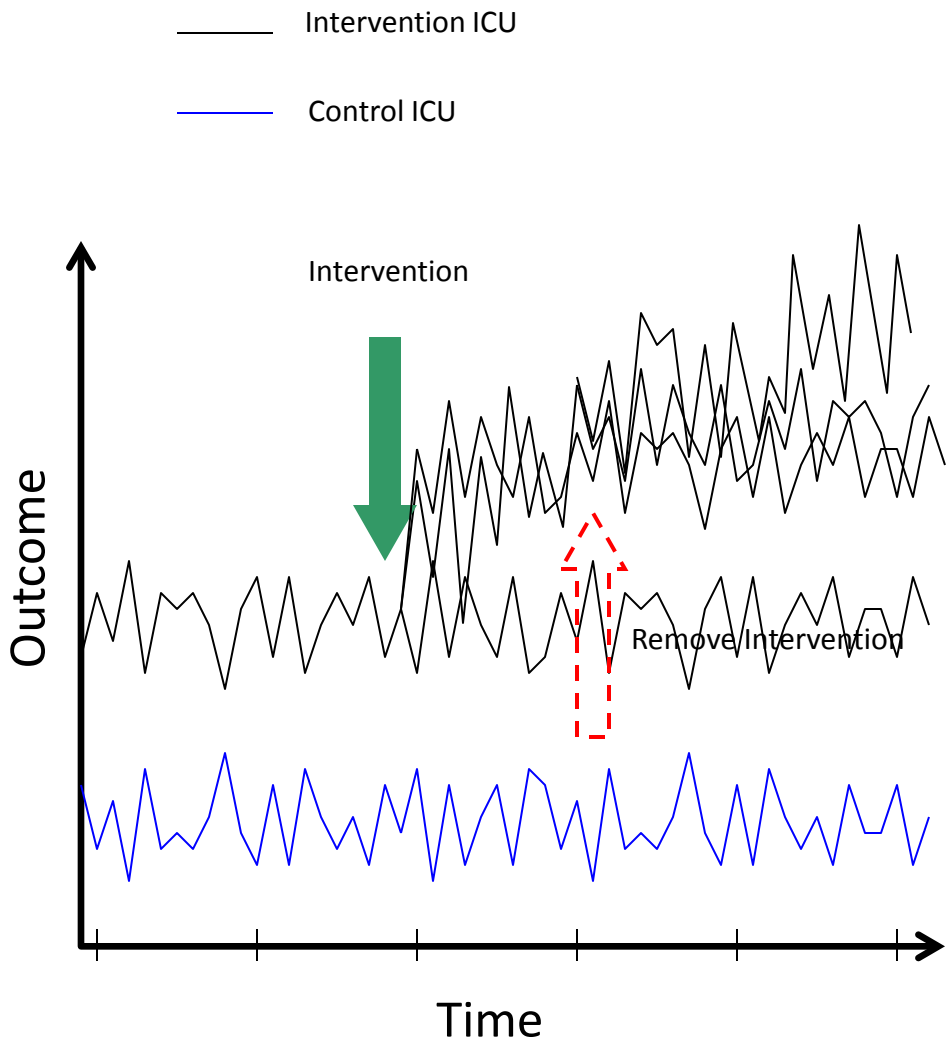
- *Non-Equivalent* Control: SICU (or Hospital B)

Interrupted Time-Series Designs

- O1 O2 O3 O4 X O5 O6 O7 O8
- Easier to control for confounding, regression to the mean, and maturation effects
- Statistically more robust analytic capabilities
  - Ability to analyze change in intercept or in slope
  - Segmented regression
- General rule: 20 points before, 20 points after*

***Crabtree BF et all J Clin Epidemiol 1990**

Time Series Variations



- Baseline Observations
- Intervening may
  - Do Nothing
  - Change the intercept
  - Change the slope
- Remove Intervention
- Add Nonequivalent Control Group

Quasi-Experiment vs. RCT

- Average effect size detected is much lower in QE vs. RCTs - modest intervention benefit may be missed by QE but detected by RCT[1]
- Uncontrolled before-after QE studies overestimate the effect of an intervention compared to controlled QE studies[2]

- <u>Always use a non-equivalent control</u>

1. Heinsman DT and Shadish WR, NIDA Res Monogr. 1997
2. Lipsey MW and Wilson DB. Am Psychol. 1993

What to do? Only RCTs?

- MacLehose RR et al. National (UK) Coordinating Centre for Health Technology Assessment – "Systematic review of comparisons of effect sizes derived from randomized and non-randomized studies" 2000
- #1 Recommendation: Reviewed QE studies were of poor quality (conduct and reporting). Given that it is possible to complete high-quality QE studies, "the use of QE designs to evaluate healthcare interventions should not rejected on the basis of past QE study evidence."
- Response: Do better QE studies! (with control groups)

Quasi-Experimental Study Example

Benefits of Universal Gloving on Hospital-Acquired Infections in Acute Care Pediatric Units

Jun Yin, Marin L. Schweizer, Loreen A. Herwaldt, Jean M. Pottinger and Eli N. Perencevich

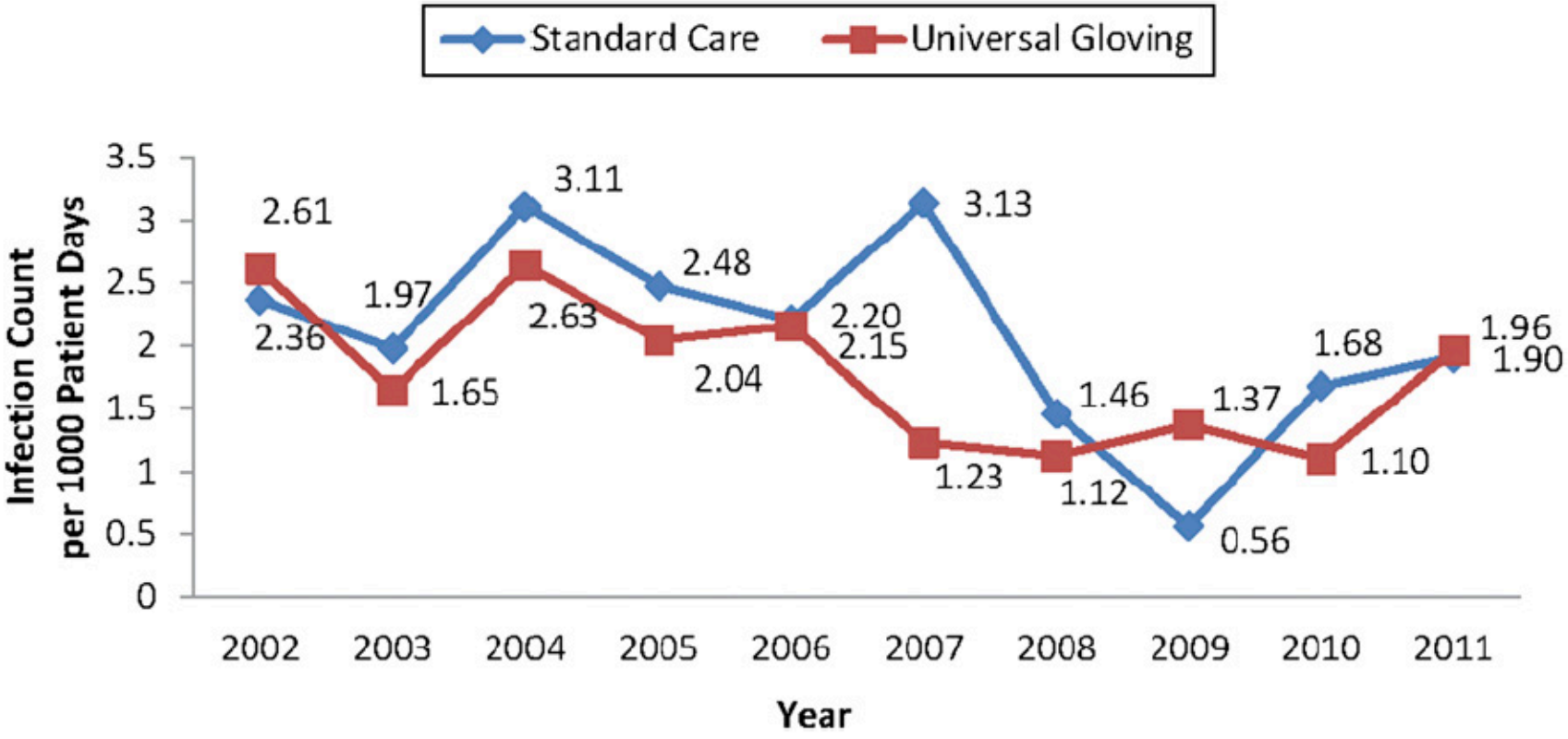
Pediatrics; originally published online April 22, 2013;
DOI: 10.1542/peds.2012-3389

- In addition to hand hygiene, glove use may reduce infections in healthcare settings
- Univ. Iowa mandates gloves during RSV season
- **Aim: Determine the impact of universal gloving on HAI in pediatric inpatient units**

Methods

- Quasi-experimental study with Poisson regression models (2002-2010)
- 5 peds units: PICU, NICU, BMT, Heme-Onc & Med/Surg Wards
- Exposure: mandatory glove period vs. periods of standard practice
- Outcome: infection rates per 1000 patient days

Universal Gloving in Pediatrics



Reference: Yin J et al. Pediatrics 2013

Overall Results

- Universal gloving periods:
- **25% reduction in HAI rates, p=0.01**
  - 37% reduction in bloodstream infections (RR=0.63, p<0.01)
  - 39% reductions in CLABSI (RR=0.61, p<0.01)

Study Networks

- VA-funded infection prevention study network
  - National System with 130 hospitals
  - Standardized electronic health records
    - Microbiology, ADT, Pharmacy
- 10 hospital network
  - Research assistants funded at each site for 5 years
  - Multiple cluster-randomized and QE studies
- Remaining 120 hospitals are controls

Study Designs for Population-level Interventions

- Quasi-experimental study designs
- **Mathematical models to simulate interventions**
- Cluster-randomized trials

Mathematical Model

MAJOR ARTICLE

Projected Benefits of Active Surveillance for Vancomycin-Resistant Enterococci in Intensive Care Units

Eli N. Perencevich,[1,2] David N. Fisman,[3] Marc Lipsitch,[4] Anthony D. Harris,[1,2] J. Glenn Morris, Jr.,[1,2] and David L. Smith[2]

[1]Veterans' Affairs Maryland Healthcare System, and [2]Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, Maryland; [3]Department of Epidemiology and Biostatistics, School of Public Health, Drexel University, Philadelphia, Pennsylvania; and [4]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts

(See the editorial commentary by Farr on pages 1116–8)

Perencevich, et al. Clin Infect Dis 2004; 38-1108-15

Example Model

- Simulated active surveillance in 10-bed ICUs
  - 1000 1-year simulations ~ 1000 clinical trials
- Parameters identified through systematic review
- Vary model parameters to project impact of active surveillance in variety of settings:
  - Community vs. tertiary care centers
  - High vs low-prevalence hospitals

Generalizability – Sensitivity Analysis

Variable name and value	Estimated no. of incident cases of VRE colonization/infection prevented with AS compared to no surveillance	Reduction of cases of VRE colonization/infection with AS, %
Base case AS benefits if patient is isolated after culture results are determined to be positive	45.8	39
ICU occupancy, %		
90	40.0	40
80	30.8	40
Transmission probability		
0.0125	23.2	44
0.05	61.9	25
Length of ICU stay, mean days		
2	18.5	29
8	40.8	27
Prevalence of VRE colonization at admission, %		
5	9.9	44
10	34.2	42
30	49.4	37
50	43.1	35

Cluster-randomized trials

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Targeted versus Universal Decolonization to Prevent ICU Infection

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Jason Hickok, M.B.A., R.N., Ta
Leah Terpstra, B.A., Fallon Hartford, M
Victoria J. Fraser, M.D., Katherine H
Jonathan B. Perlin, M.D., Ph.D
and the AHRQ DECI

Research

Original Investigation

Universal Glove and Gown Use and Acquisition of Antibiotic-Resistant Bacteria in the ICU
A Randomized Trial

Anthony D. Harris, MD, MPH; Lisa Pineles, MA; Beverly Belton, RN, MSN; J. Kristie Johnson, PhD; Michelle Shardell, PhD; Mark Loeb, MD, MSc;
ıD; Eli N. Perencevich, MD, MS; Kendall K. Hall, MD, MS;
JGG) Investigators

Effect of Influenza Vaccination of Children on Infection Rates in Hutterite Communities
A Randomized Trial

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Julie Fox, PhD
David J. D. Earn, PhD

Context Children and adolescents appear to play an important role in the transmission of influenza. Selectively vaccinating youngsters against influenza may interrupt virus transmission and protect those not immunized.

Objective To assess whether vaccinating children and adolescents with inactivated influenza vaccine could prevent influenza in other community members.

Design, Setting, and Participants A cluster randomized trial involving 947 Canadian children and adolescents aged 36 months to 15 years who received study vac-