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Clostridium difficile Colonization in Ontario (COLON): Acute Care Hospital Pilot Feasibility Study, Preliminary Findings

Johnstone J, Broukhanski G, Adomako K, Nadolny E, Katz K, Vermeiren C, Ciccotelli W, Young P, McGeer A, Bartoszko J, Chau D, Rosella L, Daneman N, Weese S, Allen V, Garber G.

September 28, 2017

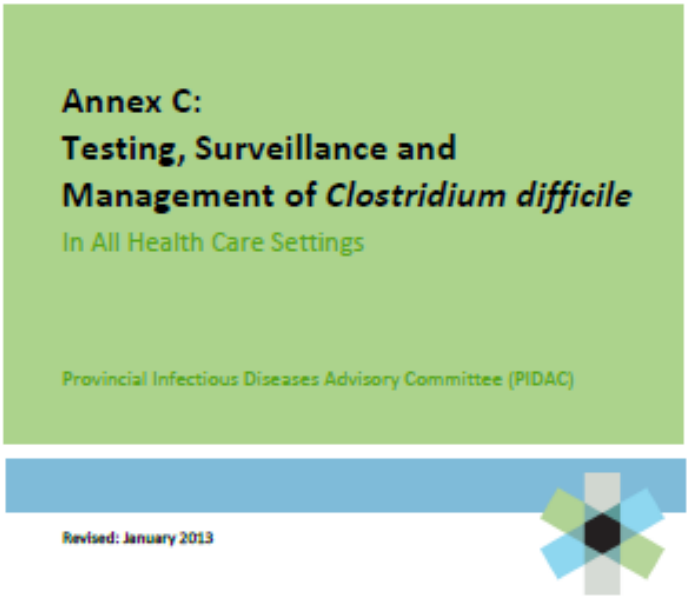
Ontario
Agency for Health Protection and Promotion
Agence de protection et de promotion de la santé

Background

- Healthcare associated *Clostridium difficile* infection is associated with significant morbidity and mortality.
- Preventing healthcare associated *C. difficile* is an important patient safety priority in Ontario.
- Hospitals in Ontario have been reporting C. difficile infection rates since 2008.
- *C. difficile* outbreaks in hospitals and long-term care homes are reportable.

Prevention of Healthcare Associated *C. difficile*

- Current prevention efforts only focus on symptomatic *C. difficile infection*
- No guideline recommendations to test patients for C. difficile colonization
- Even if colonization is detected, no IPAC measures are implemented



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C. difficile Colonization as a Reservoir for Infection

- Increasingly, *C. difficile* colonization is recognized as a potential source of healthcare associated *C. difficile*.

- Colonization estimates on admission to hospital range from 0% - 21%.

- Potentially only ~1/3 of nosocomial *C. difficile* infection can be linked to another person with *C. difficile* infection.

Eyre D et al. N Engl J Med 2013; 369: 1195 – 1205.

Research

Original Investigation | LESS IS MORE

Hospital Ward Antibiotic Prescribing and the Risks of *Clostridium difficile* Infection

Kevin Brown, PhD; Kim Valenta, PhD; David Fisman, MD, MSc; Andrew Simor, MD; Nick Daneman, MD, MSc

JAMA Intern Med. 2015;175(4):626-633.

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Receipt of Antibiotics in Hospitalized Patients and Risk for *Clostridium difficile* Infection in Subsequent Patients Who Occupy the Same Bed

Daniel E. Freedberg, MD, MS; Hojjat Salmasian, MD, PhD; Bevin Cohen, MPH; Julian A. Abrams, MD, MS; Elaine L. Larson, RN, PhD

JAMA Intern Med. 2016;176(12):1801-1808

Original Investigation

June 2016

Effect of Detecting and Isolating *Clostridium difficile* Carriers at Hospital Admission on the Incidence of *C difficile* Infections

A Quasi-Experimental Controlled Study

Yves Longtin, MD[1,2]; Bianka Paquet-Bolduc, RN, MPA[3]; Rodica Gilca, MD, PhD[4,5,6]; et al

» Author Affiliations

JAMA Intern Med. 2016;176(6):796-804. doi:10.1001/jamainternmed.2016.0177

Unanswered Questions

- Who is at risk of *C. difficile* colonization
  - Does this differ between healthcare associated and non-healthcare associated *C. difficile* colonization
- What strains are involved?
  - Does this differ between healthcare associated and non-healthcare associated colonization?
- What is the natural history of patients with *C. difficile* colonization
- Does the risk of *C. difficile* infection according to colonization status (e.g. non-colonized, toxigenic strain colonized, non-toxigenic strain colonized).

- More information about the epidemiology, microbiology and natural history of patients colonized with *C. difficile* upon admission to acute care hospital is needed to inform future infection prevention and control interventions.

Johnstone J *et al.* AMMI Canada Conference May 4, 2017 Toronto, ON

COLON: ACUTE CARE HOSPITAL PILOT FEASIBILITY STUDY

Need for a feasibility study

- A large multi-center provincial study of *C. difficile* colonization is needed;
- Complex coordination required between Public Health Ontario, Public Health Ontario Laboratories (PHOL), hospital sites and ICES;
- A pilot study needed to ensure:
  - Feasibility;
  - Identify and eliminate potential barriers to scaling up a large study;
  - Ensure hospital and PHOL standard operating procedures are efficient and clear;
  - Provide critical data needed to inform sample size calculations.

Objectives of this feasibility study

1. Determine the feasibility of testing for *C. difficile* using consecutive antimicrobial resistant organism (ARO) screening swabs obtained from patients as part of usual care;
2. Determine the proportion of ARO screening swabs positive for *C. difficile* and their strain types;
3. Through linkage with ICES, determine the proportion of patients colonized with *C. difficile* on admission to hospital and stratify the results by healthcare associated versus community acquired.

Methods

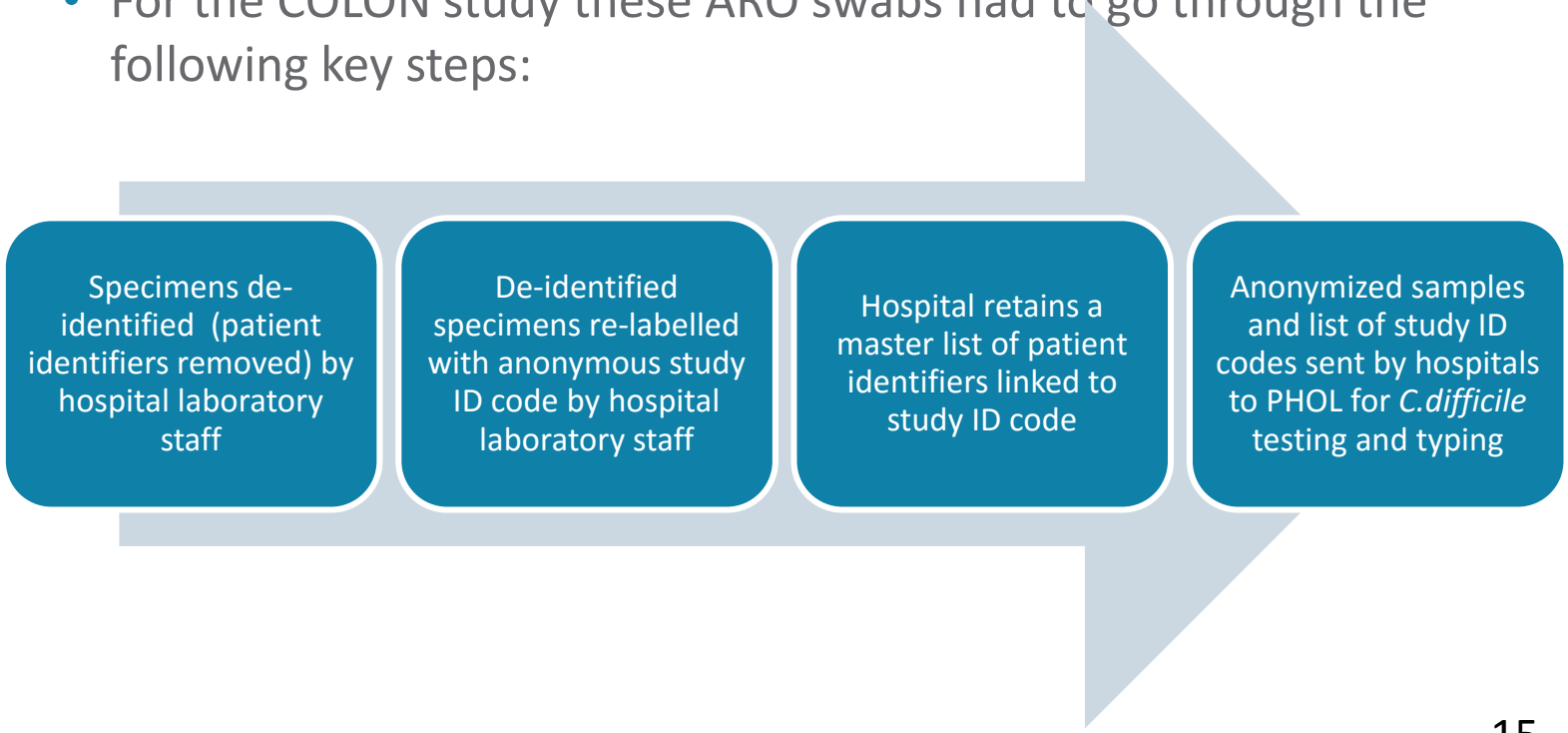
- Prospective cohort study
- Consecutive ARO rectal swabs received by hospital laboratories from patients admitted to one of 3 acute care hospitals in Ontario over a period of 1 month
- De-identified ARO swabs sent to PHOL for testing
- Linkage of ARO swab results to ICES

The Context

- Study design required 2 separate but linked approaches:
  - **Part A**-collection and de-identification of ARO screening swabs sent by participating hospitals to PHOL for *C. difficile* testing and typing
    - Partnership between PHO, PHOL, and 3 acute hospitals
  - **Part B**- OHIP numbers for each sample sent to PHOL to be sent by hospitals to ICES; individual *C. difficile* testing and typing results sent by PHOL to ICES; ICES to perform linkage with ICES administrative databases using OHIP numbers received from hospitals matched to *C. difficile* testing and typing results received from PHOL
    - Partnership between PHO, PHOL, 3 acute hospitals in Ontario, and ICES

Part A-The Plan

- Collection of consecutive ARO screening swabs for a period of 1 month from 3 hospitals
- ARO screening swabs are labelled with patient identifiers (e.g. name, MRN) when the specimen is collected for their intended use
- For the COLON study these ARO swabs had to go through the following key steps:



The Dilemma

- For Part A of the COLON study: Is the use of ARO swabs for research purposes without obtaining patient consent for use of those swabs ethical?
- Generated debate at the 3 acute hospitals and PHO REBs
  - Could patients be informed by a nurse at time of swab collection that it would be used after ARO screening purposes for a research study? Was this feasible?
  - In the absence of a hospital policy on secondary use of swabs, how would a hospital determine if this was an appropriate use of the swab?
  - Are the *C. difficile* spores that might be detected considered human biological materials?
  - Would a patient be at risk if *C. difficile* was detected on their swab? Was their a clinical impact that would be unethical to inform patients of the *C. difficile* testing and typing results?
  - Would a study flyer or notification about the study displayed in patient areas be a possible strategy for informing potential study participants?

The Context

- Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2)
  - The three Agencies: Canadian Institutes of Health Research; Natural Sciences and Engineering Research Council of Canada; Social Sciences and Humanities Research Council of Canada

- TCPS 2 is the benchmark in Canada for ethical conduct of research involving humans and is used by all REBs in Canada to guide ethical reviews of research projects

- As a condition of funding, the Agencies require that researchers and their institutions apply the ethical principles and the articles of TCPS 2 and be guided by the application sections of the articles.

The Dilemma

- TCPS 2 articles related to the questions generated through ethics reviews:
  - *12. B Collection of Human Biological Materials* –CONSENT REQUIRED
  - *12 C. Consent and Secondary Use of Identifiable Human Biological Materials for Research Purposes-CONSENT CAN BE WAIVED*

- The main issue:
  - Were the swabs being collected for dual purposes at the time of collection (routine screening and the COLON study)? If so, does this constitute secondary use allowing for consent to be waived?

- Prior to REB submissions we held consultations with ethics and privacy officers at various hospitals and contacted TCPS 2 directly for clarification

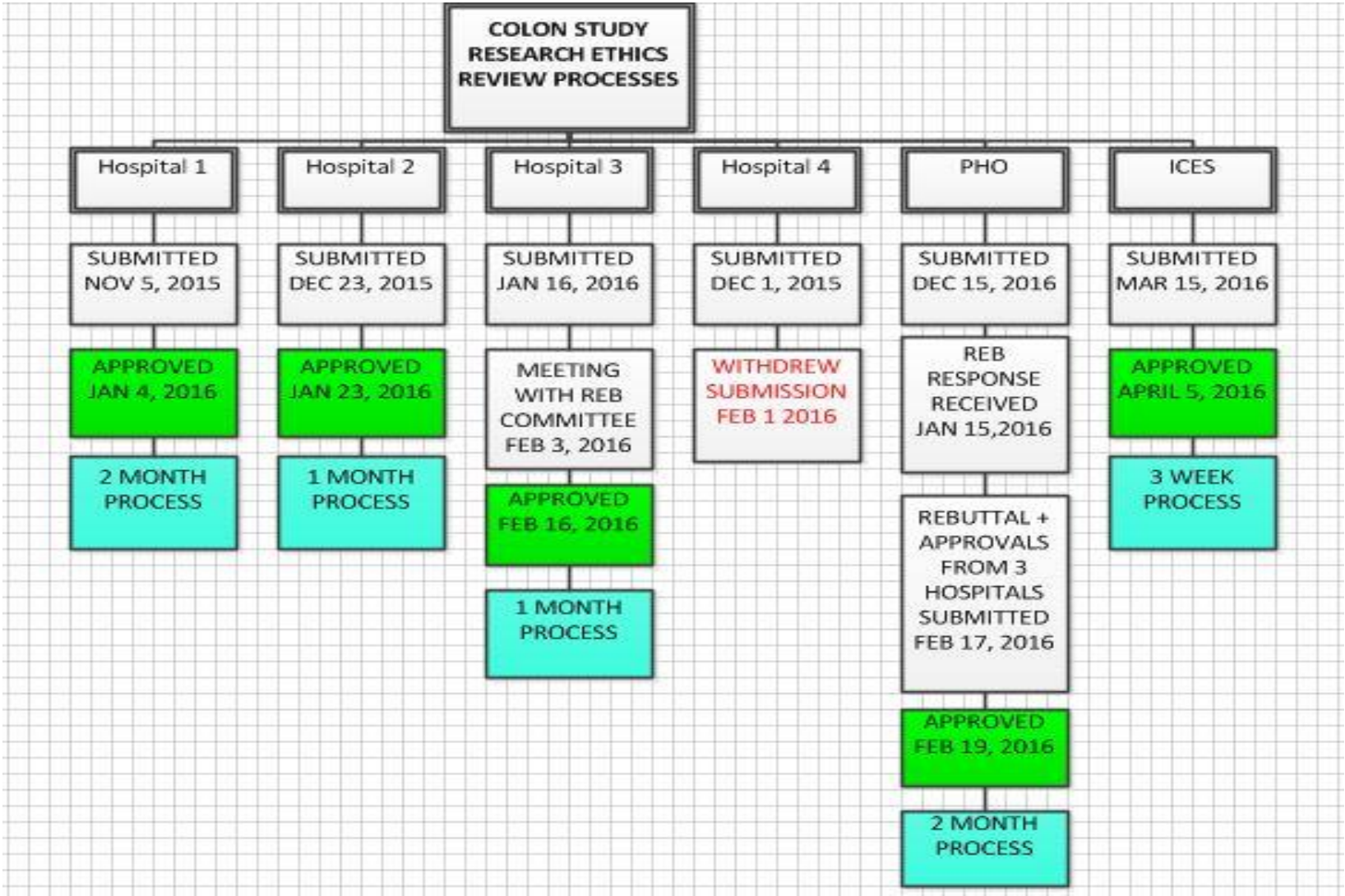
TCPS 2-Article 12-Consent Waiver

- Article 12.3A Researchers who have not obtained consent from participants for secondary use of identifiable human biological materials shall only use such material for these purposes if they have satisfied the REB that:
- a. identifiable human biological materials are essential to the research;
- b. the use of identifiable human biological materials without the participant's consent is unlikely to adversely affect the welfare of individuals from whom the materials were collected;
- c. the researchers will take appropriate measures to protect the privacy of individuals and to safeguard the identifiable human biological materials;
- d. the researchers will comply with any known preferences previously expressed by individuals about any use of their biological materials;
- e. it is impossible or impracticable to seek consent from individuals from whom the materials were collected; and
- f. the researchers have obtained any other necessary permission for secondary use of human biological materials for research purposes.

The Outcome

- Application of consent process should be related to relative risk of a study; determined on a case-by-case basis by each REB
- All 3 acute hospitals agreed that section 12 C could be applied to the COLON study and agreed that consent could be waived due to impracticality of obtaining consent and no clinical impact of *C. difficile* testing and typing results
- The REB from the fourth potential acute hospital required further discussion and debate before reaching a decision; due to increasing project timeline pressures decision was made to withdraw the submission and conduct the study at 3 instead of 4 acute hospitals
- PHO deferred consent issue for the hospital REBs to decide; once hospitals agreed PHO would approve

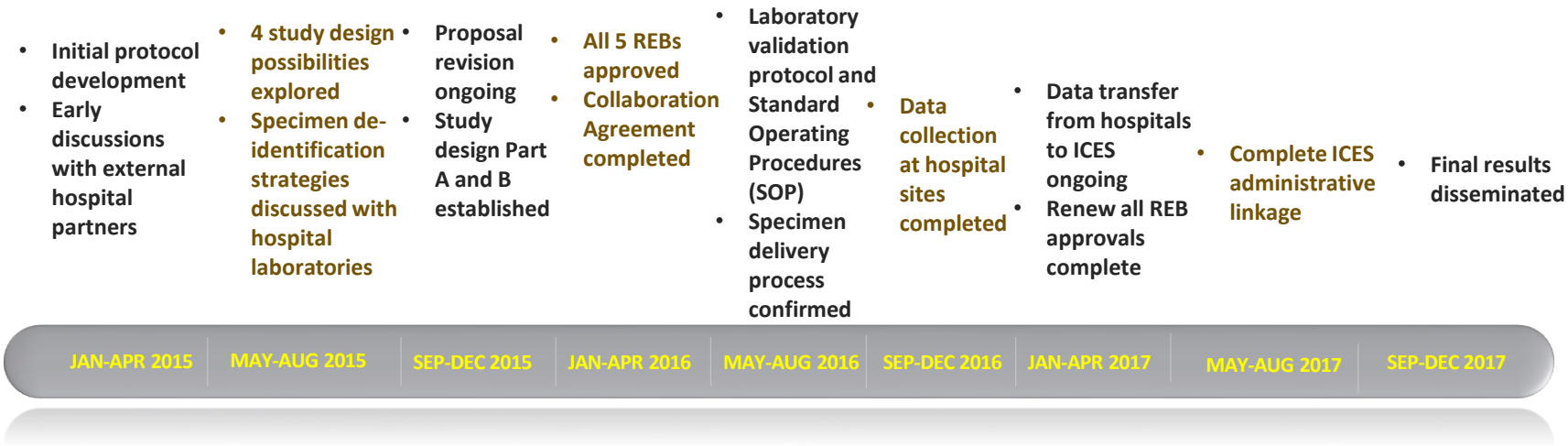
COLON REB Map



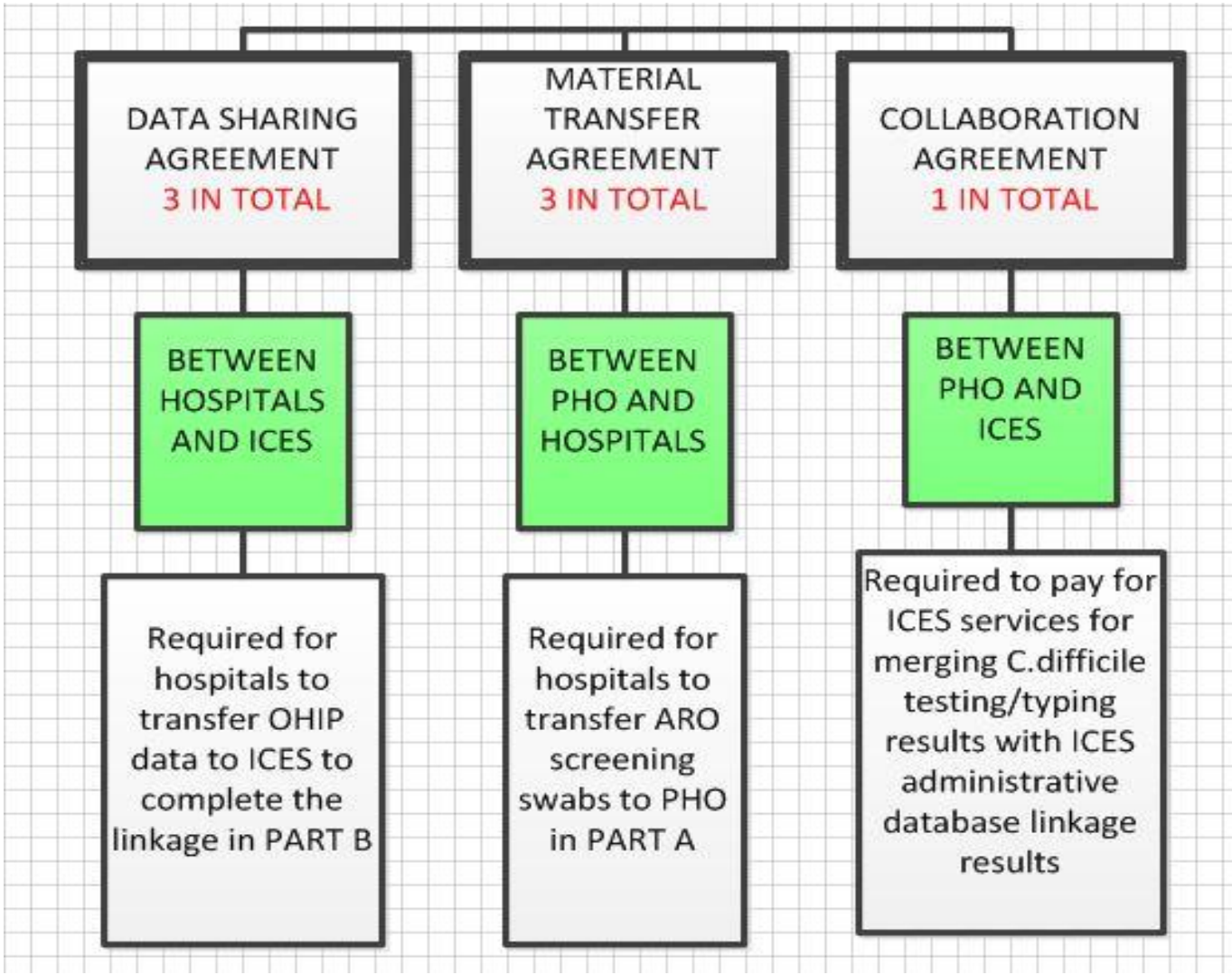
REB: Lessons Learned

- Secretariat on Responsible Conduct of Research can help with interpretations of TCPS 2
- Ethics and Privacy considerations can change your original research design
  - E.g. ICES required Part A and Part B to be separate since their Privacy Impact Assessment can only be used for 1 data disclosure at a time; PHOL disclosing *C. difficile* testing and typing results to ICES (Part A) vs hospitals disclosing OHIP numbers to ICES (Part B)
- Sequence of REB submissions makes a difference
  - Approvals from hospitals with more established REBs (e.g. Mount Sinai) can be used to leverage approvals from hospitals with less established REBs (e.g. Grand River)

COLON Project Timeline



Legal Agreements



Part A-The Plan

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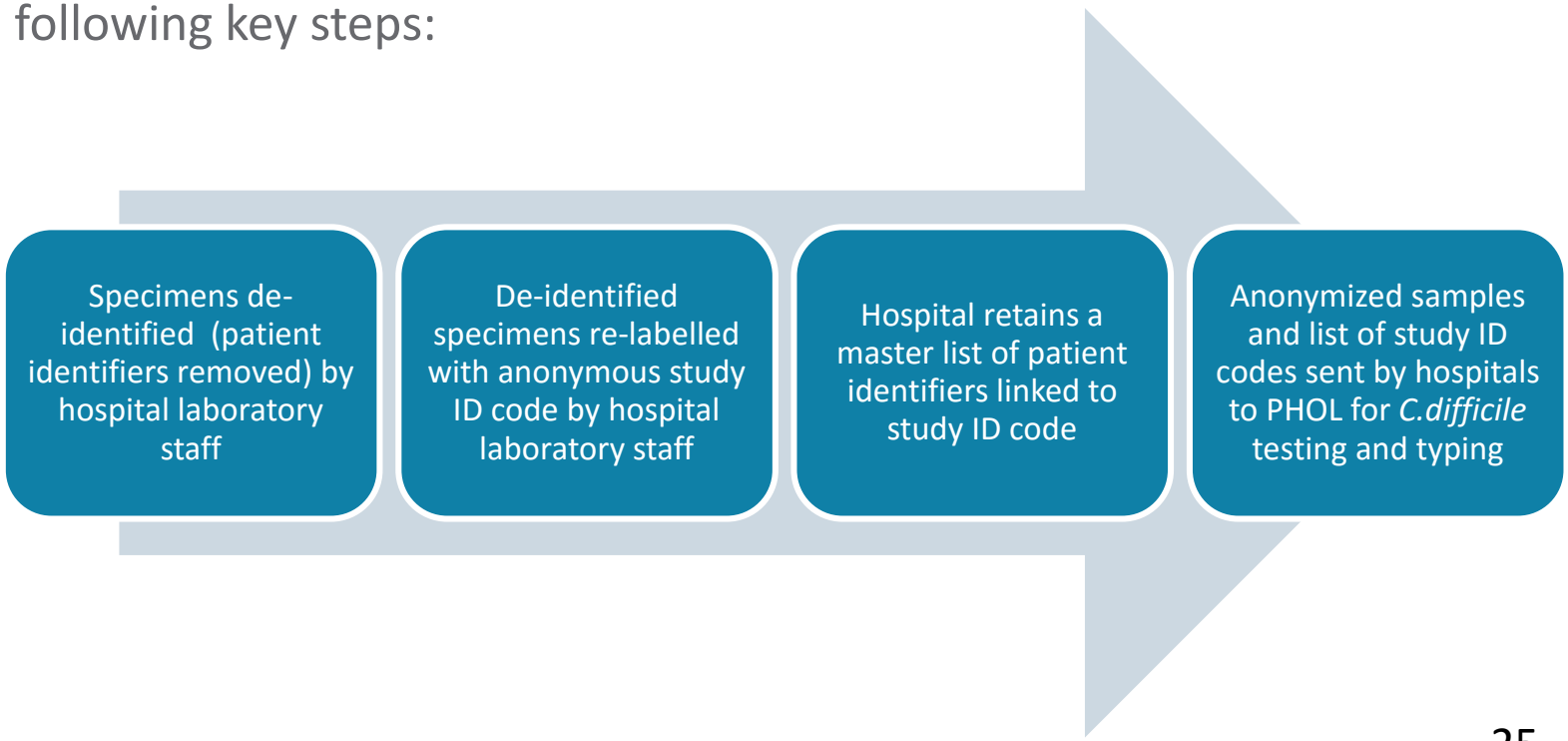

Operational: Specimen de-identification and labelling

Clostridium difficile colonization in Ontario (COLON): Acute Care Hospital Pilot Feasibility Study
COLON Study- Grand River Hospital

COLON STUDY-SPECIMEN MANAGEMENT STEPS

The following is a guide to assist you preparing specimens for shipment to the Public Health Ontario Laboratory (PHOL).

COLON Study Specimen Toolkit- Participating hospital sites will receive the following from PHO:

- 1500 study ID barcode stickers (3 sets of the same study ID for each specimen)
- 1500 colored stickers for de-identification (3 sets of stickers covering each specimen tube)
- 2 pre-labelled red specimen delivery bags
- 4 Clear Plastic Specimen Containers
  - 2 containers per specimen delivery bag

Directions for each specimen

Note: Please ensure all specimens included in this process are no longer needed at your facility. The specimens will NOT be returned.

1. In advance, print from the lab IS department the Master Study Report with the following columns: Study ID (this column will be blank), PID, Health Card Number, Accession Number, Order Location, and Date. Also print the Modified Study Report that will have Study ID (this column will be blank), Accession Number, Order Location, and Date. The completed Modified Study Report will be included in the red specimen delivery bag shipped to PHOL.
2. Place 1 study ID barcode sticker in the blank study ID column on the Master and Modified lab IS report.
3. Use 3 of the colored de-identification stickers to completely cover the specimen tube.
4. Ensure no identifying information is visible on the specimen after Step 3.
5. Place 3rd study ID barcode sticker on the de-identified specimen tube.
6. Double check to ensure study ID barcode on the de-identified specimen tube matches the study ID barcode in the corresponding row on the Master and Modified lab IS report.
7. Batch de-identified specimens and place in a plastic biohazard bag which can be placed inside the clear plastic specimen storage containers provided and store at 2-8°C following collection and prior to shipping.
8. Make a photocopy of the completed Modified Study Report and put the original in a plastic biohazard and place inside the red specimen bag prior to shipment.
   a. The original Master and copy of the Modified lab IS report is kept by the site PI.
9. Place 2 clear plastic specimen containers in each pre-labelled red specimen delivery bag.
10. Ship red specimen delivery bags to PHOL as per routine laboratory delivery methods.
    Once received at PHOL your delivery will be inspected to ensure de-identification methods were completed appropriately and the same red specimen delivery bags will be sent back to your facility to repeat the process. Specimen batches should be sent a minimum of once per week for the duration of the data collection period (June 7-July 7).

For questions about this process, your shipment, or to order additional labels please contact:

Kwaku Adomako; Public Health Ontario; Email: Kwaku.adomako@oahpp.ca; Tel: 647-260-7219

Emily Nadolny; Public Health Ontario; Email: Emily.nadolny@oahpp.ca; Tel: 647-260-7572

COLON STUDY-SPECIMEN DE-IDENTIFICATION STEPS

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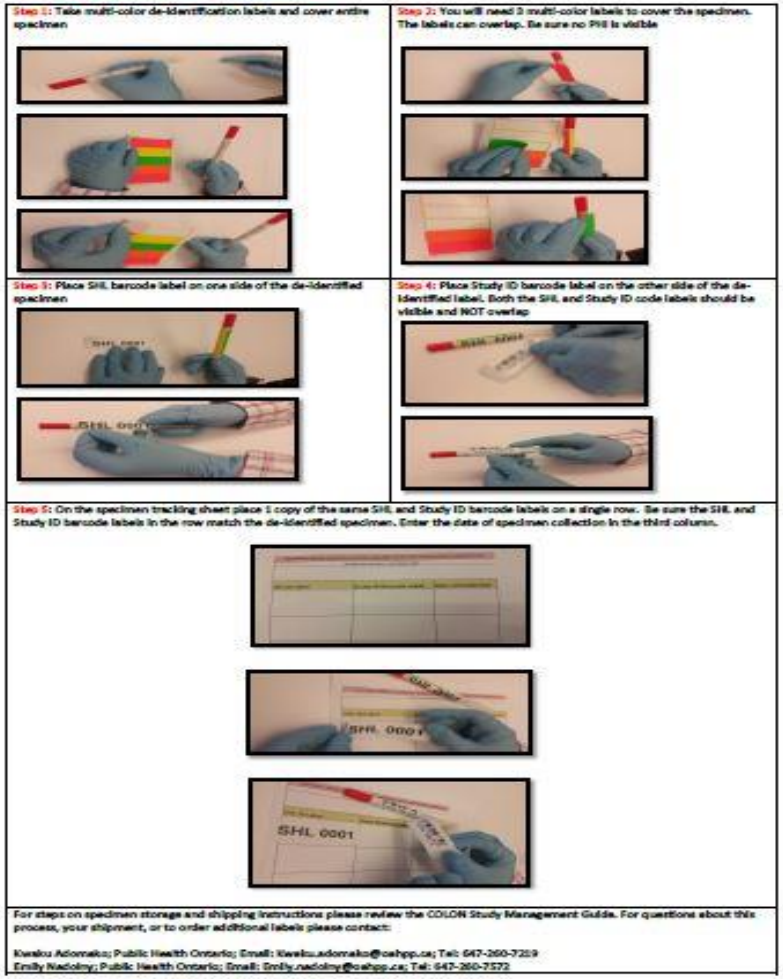


Operational: Specimen Delivery

ATTENTION!

PHO COLON STUDY-SPECIMEN DELIVERY INSTRUCTIONS

PLEASE BE AWARE THAT FROM JUNE 22 TO AUGUST 15 PHOL WILL BE RECEIVING WEEKLY SPECIMENS FOR THE COLON STUDY FROM 3 HOSPITALS:

THE COLON STUDY SPECIMENS WILL BE SHIPPED/RECEIVED IN DISTINCT RED SPECIMEN BAGS THAT WILL BE ADDRESSED TO DR. GEORGE BROUHANSKI.:

ANY QUESTIONS CONTACT STUDY COORDINATOR **KWAKU ADOMAKO**-647-260-7219/KWAKU.ADOMAKO@OAHPP.CA OR **EMILY NADOLNY** -647-260-7572/EMILY.NADOLNY@OAHPP.CA

THANK YOU FOR YOUR SUPPORT WITH THE COLON STUDY!

Methods

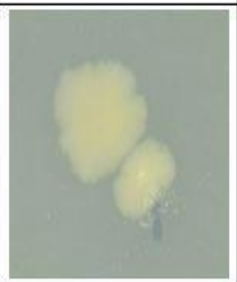
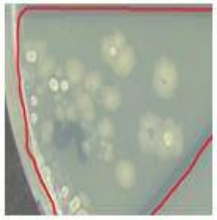
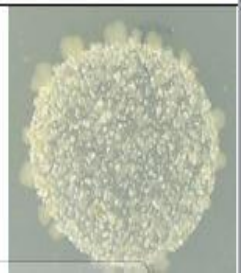
- Isolation of *C. difficile* culture was performed by direct inoculation of *C. difficile* CHROMagar
  - 100 specimens also placed in an enrichment broth (Cycloserine Cefoxitin Mannitol Broth with Taurocholate and Lysozyme)
- DNA was extracted from 4 colonies per isolate confirmed as *C. difficile* to identify if multiple strains are present

Methods

- Molecular identification and typing done by ribotyping and Modified Multiple-Locus Variable-number tandem repeat analysis (MMLVA)
- Ribotypes were identified using an on-line database
- NAP was inferred based on ribotyping results

Validation Protocol-Laboratory Procedures

Experiment 1: Swab Testing

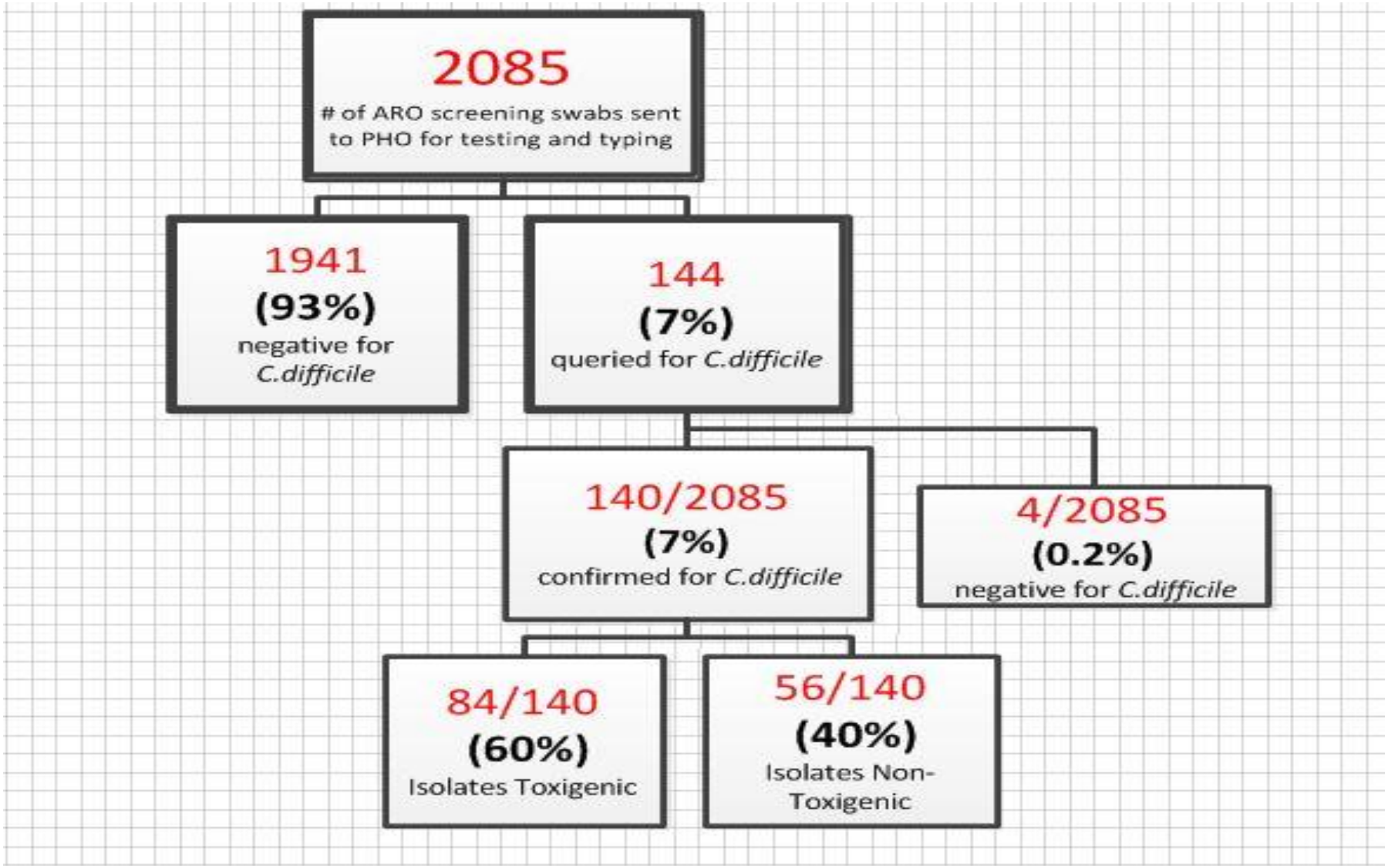
	Swab Type				QC		
Specimen Number	Aimes Charcoal (48 Hours)	Starplex Gel (48 Hours)	Copan UTM Liquid (48 Hours)	Copan UTM Liquid Enrichment (48 Hours)	In Sectors Streaked with 10 uL Loop (48 Hours)	10 uL smear onto Plate (48 Hours)	50 uL Drop onto Plate (72 Hours)
1							
2							
3							

Results

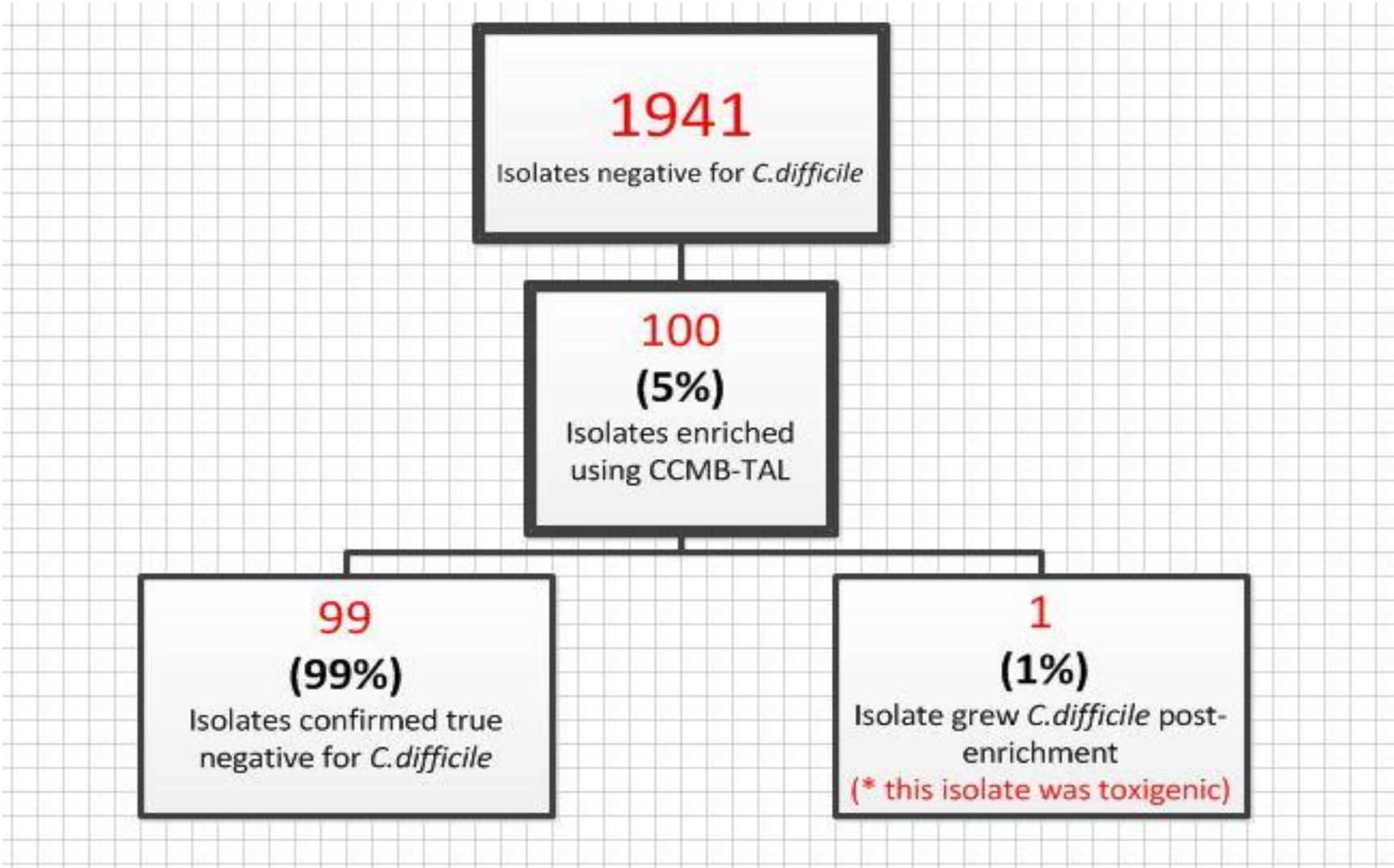
- In total, 2692 ARO screening swabs were routinely collected during the study period

- Of these, 2085 (77%) were sent to the reference laboratory
  - Hospital 1: 649/685 (95%)
  - Hospital 2: 835/855 (98%)
  - Hospital 3: 601/1152 (52%)

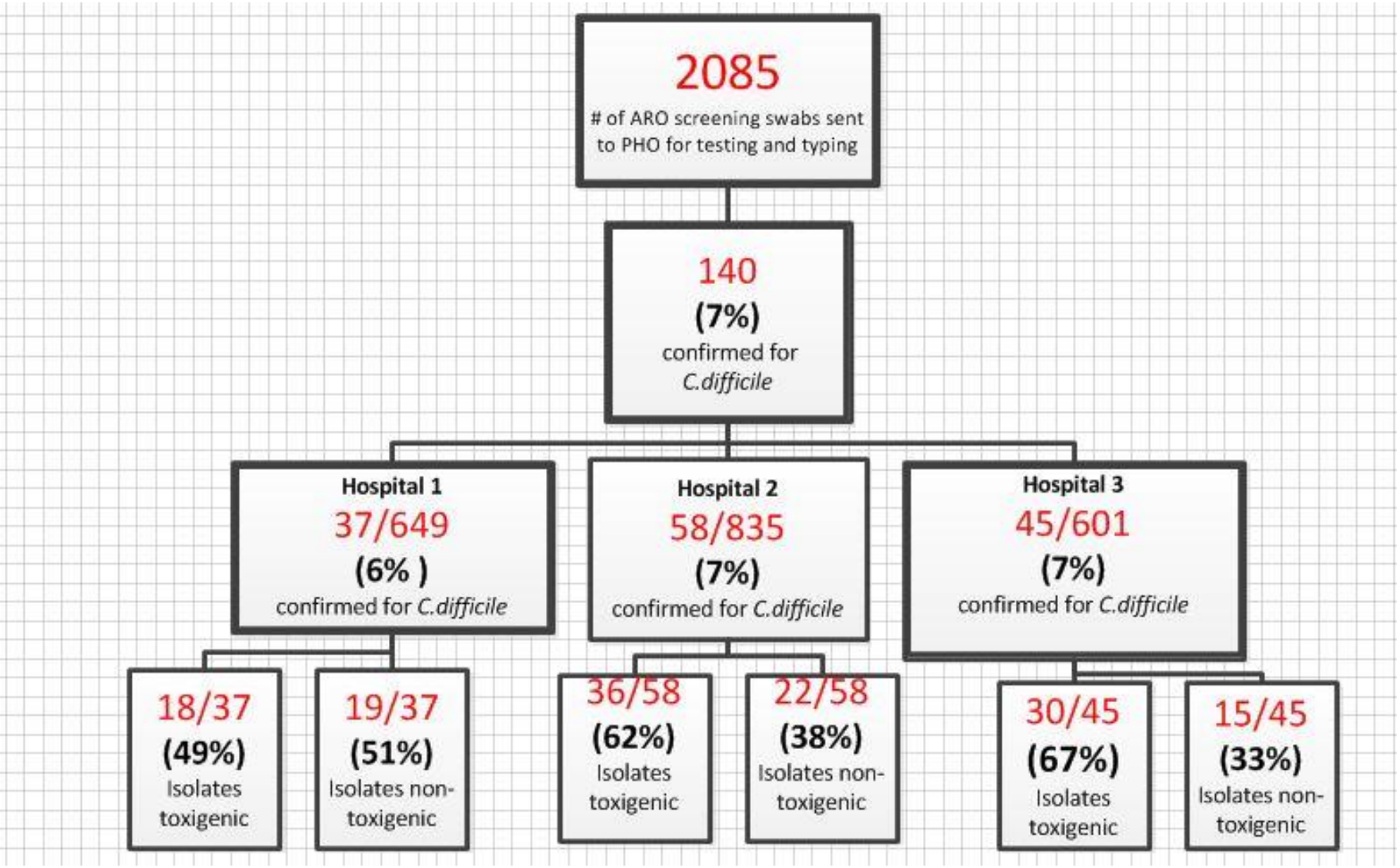
Overall Results



Enrichment Results

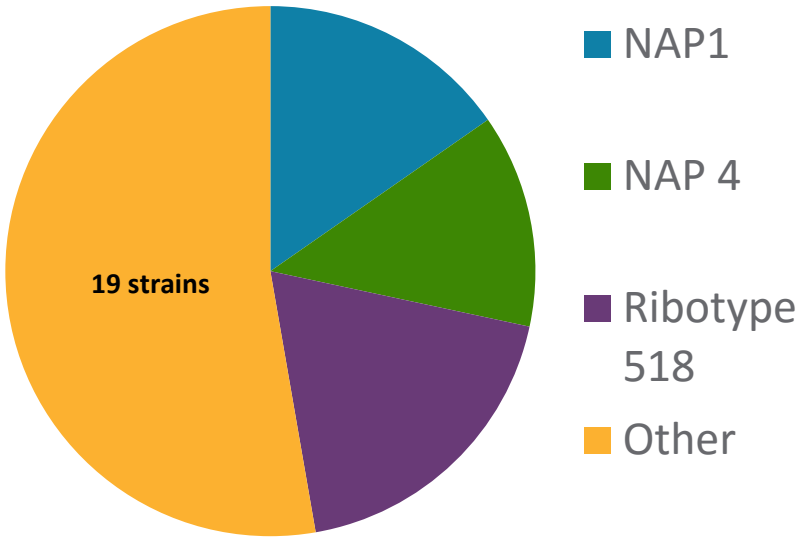


Hospital Results

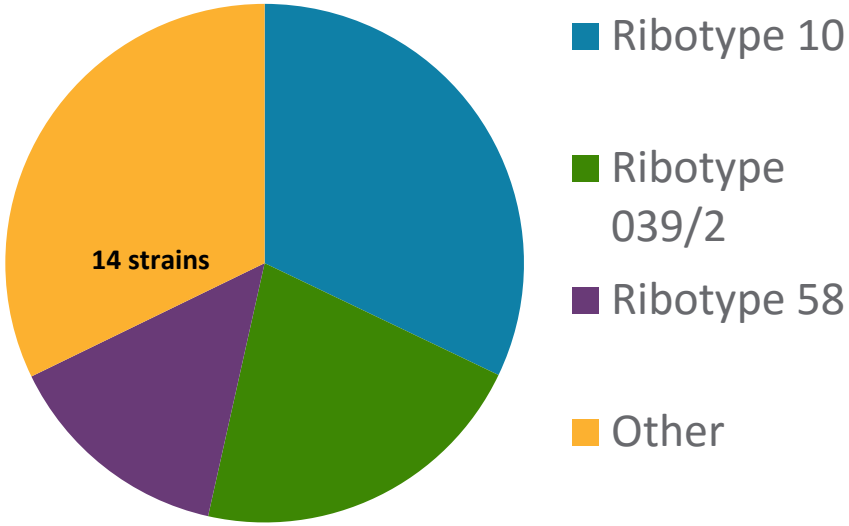


C. difficile strain types

Toxigenic



Non-toxigenic



Conclusions

- Use of routinely collected ARO screening rectal swabs from the detection of *C. difficile* colonization is feasible
  - Sufficient human resources and work flow integration are essential in maximizing proportion of ARO swabs sent to the reference laboratory
- *C. difficile* was present in 7% of patients in this study, including toxigenic strains and non-toxigenic strains
  - Enrichment broth did not materially increase the yield
  - Results were consistent across hospitals
  - NAP-1, NAP-4, Ribotype 58 were the most common toxigenic strains

Next Steps

- Results will be linked to ICES data
  - 1752/2085 (84%) patients linked, and duplicates removed
  - 1308/1752 (75%) represented swabs upon admission to hospital
  - N=1308 will be the final study sample for the ICES linkage portion

Next Steps

- Goals will be to determine:
- Proportion of admitting ARO screening swabs positive for *C. difficile*;
- Stratify *C. difficile* by community acquired versus healthcare acquired *C. difficile*;
- Describe the natural history of patients with *C. difficile* colonization and determine the risk of *C. difficile* infection according to colonization status (e.g. non-colonized, toxigenic strain colonized, non-toxigenic strain colonized).

Questions?