Antimicrobial Stewardship:

A Call to Action

Kevin Schwartz MD MSc FRCPC
Physician, IPAC/Antimicrobial Stewardship, Public Health Ontario
Assistant Professor, DLSPH, University of Toronto
Adjunct Scientist, Institute for Clinical Evaluative Sciences
Div. of Infectious Diseases, St. Joseph’s Health Centre, Toronto
Objectives

• To review the current state of antimicrobial resistance
• Describe how Antimicrobial Stewardship is a patient safety issue
• Explain why ASP and IPAC need to work together
• Describe the antimicrobial stewardship program (ASP) at Public Health Ontario
Antimicrobial Resistance Requires Global Action

“AMR...is a slow-motion tsunami. It is a global crisis that must be managed with utmost urgency”.

AMR is the “greatest and most urgent global risk”.

“AMR is a serious and growing public health threat”
CANADIAN ANTIMICROBIAL RESISTANCE SURVEILLANCE SYSTEM – REPORT 2016
Gonorrhea

Percentage of gonorrhea isolates resistant to antibiotics, 2004 to 2014

- Penicillin Resistance
- Tetracycline Resistance
- Erythromycin Resistance
- Ciprofloxacin Resistance
- Azithromycin Resistance
- Cefixime Resistance
- Ceftriaxone Resistance
MRSA

Figure 12: National MRSA infection rates, 1995 to 2014

- Infection rate per 1,000 patient admissions
- Infection rate per 10,000 patient days
CPE

Figure A: Carbapenemase-producing Enterobacteriaceae (CPE) in Canada: the Canadian Public Health Laboratory Network (CPHLN) data, 2008 to 2014

![Graph showing the number of isolates of CPE over years from 2008 to 2014. The graph indicates an increasing trend for KPC, NDM, OXA-48LIKE, SME, and Other types of isolates.](image-url)
E. Coli in Chickens and Pigs

Figure 31: Resistance to selected antimicrobials among generic *Escherichia coli* isolates from chicken samples collected from farms (broiler), slaughter and retail stores in Canada, 2004-2014

Figure 32: Resistance to selected antimicrobials among generic *Escherichia coli* isolates obtained from swine samples collected from farms (grower-finisher), slaughter and retailers in Canada, 2004 to 2014
How Does Resistance Occur?

- Resistance is natural
- Some bacteria inherently resistant
- Many mechanisms of resistance
- Some are inducible
- Some are constitutive
- Some are transferrable
MCR-1

- Confers colistin resistance
- A plasmid that contains the resistance complex
- Resistance genes can pass to other organisms
- Found in animal excrement, then in food supply and finally in patients
ANTIBIOTIC RESISTANCE
from the farm to the table

RESISTANCE
All animals carry bacteria in their intestines

Antibiotics are given to animals
Antibiotics kill most bacteria
But resistant bacteria survive and multiply

SPREAD
Resistant bacteria can spread to...

animal products
produce through contaminated water or soil
prepared food through contaminated surfaces
the environment when animals poop
Antimicrobial Resistance is Darwinian Selection

- Bacteria spontaneously mutate (1/10^5)

- Antibiotics provide selective pressure to mutate

- “Selection of the fittest”
Antimicrobial Use is a Driver of AMR

• Antimicrobial use is linked to antimicrobial resistance
  • Patient
  • Population

• Antimicrobial drugs are the only pharmaceutical agents that have “transmissible loss of efficacy over time”
Timeline of Antibiotic Resistance

**Antibiotic deployment**

- **Chloramphenicol**
- **Sulfonamides**
- **Penicillin**
- **Streptomycin**
- **Tetracycline**
- **Erythromycin**
- **Vancomycin**
- **Ampicillin**
- **Methicillin**
- **Cephalosporins**

**Antibiotic resistance observed**

- **1930**
- **1935**
- **1940**
- **1945**
- **1950**
- **1955**
- **1960**
- **1965**
- **1970**
- **1975**
- **1980**
- **1985**
- **1990**
- **1995**
- **2000**
- **2005**
ANTIMICROBIAL STEWARDSHIP IS ABOUT
Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis

David Bour*, Beryl Primrose Gladstone*, Francesco Burkert, Elena Carrara, Federico Foschi, Stefanie Döbele, Evelina Tacconelli

Lancet Infect Dis 2017

<table>
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<th>Event/patient-days</th>
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<td>Cruz-Rodriguez et al [27]</td>
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<td>Leung et al [22]</td>
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<td>Dubrovskaya et al [51]</td>
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<td>Cook and Gooch [37]</td>
<td>134/220474</td>
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<td>Schön et al [58]</td>
<td>182/169886</td>
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<td>Frank et al [57]</td>
<td>50/103573</td>
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<td><strong>Overall</strong></td>
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*P* = 80.2%, *p* = 0.000

Figure 4: Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of *Clostridium difficile* infections.
### Table 1: Incidence Ratios of MDR GNB before and after interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>Organism</th>
<th>Events/patient-days</th>
<th>Incidence Ratio (95% CI)</th>
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<td>Apisamthanarak et al.</td>
<td>MDR Pseudomonas aeruginosa</td>
<td>13/2889 1/1374</td>
<td>0.08 (0.00-1.41)</td>
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<td>Maria et al.</td>
<td>Imipenem-resistant Acinetobacter baumannii</td>
<td>23/8421 2/8056</td>
<td>0.09 (0.02-0.39)</td>
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<td>Apisamthanarak et al.</td>
<td>XDR A baumannii</td>
<td>33/2889 2/1324</td>
<td>0.13 (0.03-0.55)</td>
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<td>Takesue et al.</td>
<td>Metallo-β-lactamase GNB</td>
<td>27/698794 6/635794</td>
<td>0.24 (0.10-0.59)</td>
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<tr>
<td>Cook and Gooch</td>
<td>Carbapenem-resistant P. aeruginosa</td>
<td>44/220474 13/261318</td>
<td>0.25 (0.13-0.46)</td>
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<tr>
<td>Peto et al.</td>
<td>MDR P. aeruginosa</td>
<td>2/4280 1/4217</td>
<td>0.25 (0.01-5.63)</td>
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<td>Takesue et al.</td>
<td>MDR GNB</td>
<td>39/698794 10/635794</td>
<td>0.28 (0.14-0.56)</td>
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<td>Arda et al.</td>
<td>Meropenem-resistant Acinetobacter spp</td>
<td>28/285606 10/308852</td>
<td>0.33 (0.16-0.68)</td>
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<td>Leverstein-van Hall et al</td>
<td>MDR Enterobacteriaceae</td>
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<td>Yeo et al.</td>
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<td>Maria et al.</td>
<td>Imipenem-resistant Klebsiella pneumoniae</td>
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<td>0.52 (0.13-2.09)</td>
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<td>Arda et al.</td>
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<td>Meyer et al.</td>
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<td>Yeo et al.</td>
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<td>Zou et al.</td>
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<td>Niu et al.</td>
<td>Imipenem-resistant P. aeruginosa</td>
<td>11/128146 15/113873</td>
<td>1.53 (0.70-3.34)</td>
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<tr>
<td>Aubert et al.</td>
<td>Imipenem-resistant P. aeruginosa</td>
<td>49/5100 44/2548</td>
<td>1.30 (1.20-2.76)</td>
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</tbody>
</table>

**Overall**

- **P=76.2%, p=0.000**

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**Figure 2:** Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship programme on the incidence of MDR GNB

GNB=Gram-negative bacteria. MDR=multidrug-resistant. XDR=extensively drug-resistant.
IPAC + ASP = ↓ AMR

<table>
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<tr>
<th>Study setting</th>
<th>Number of studies</th>
<th>Incidence ratio (95% CI)</th>
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<tr>
<td>Intensive care unit</td>
<td>10</td>
<td>0.77 (0.66-0.89)</td>
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<tr>
<td>Medical ward</td>
<td>27</td>
<td>0.78 (0.66-0.91)</td>
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<tr>
<td>Surgical ward</td>
<td>5</td>
<td>0.76 (0.46-1.25)</td>
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<tr>
<td>Haematology- oncology ward</td>
<td>3</td>
<td>0.41 (0.20-0.85)</td>
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<tr>
<th>Co-implementation of ICMs</th>
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<tr>
<td>ASP alone</td>
<td>23</td>
<td>0.81 (0.67-0.97)</td>
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<tr>
<td>ASP + ICMs</td>
<td>9</td>
<td>0.59 (0.54-0.88)</td>
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<tr>
<td>ASP + hand-hygiene intervention</td>
<td>5</td>
<td>0.34 (0.21-0.54)</td>
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</table>

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<th>Type of intervention</th>
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<tr>
<td>Antibiotic restriction</td>
<td>15</td>
<td>0.77 (0.67-0.89)</td>
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<tr>
<td>Audits/feedback</td>
<td>19</td>
<td>0.66 (0.52-0.83)</td>
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<tr>
<td>Antibiotic cycling</td>
<td>3</td>
<td>0.49 (0.34-0.72)</td>
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<td>1980-2000</td>
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<td>2001-05</td>
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<td>2006-13</td>
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<td>Infection and/ or colonisation</td>
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<td>Infection and colonisation</td>
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<td>Infection</td>
<td>21</td>
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<td>Colonisation</td>
<td>3</td>
<td>0.72 (0.41-1.25)</td>
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<tr>
<td>Study design</td>
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<td>Interrupted time-series studies</td>
<td>6</td>
<td>1.20 (0.97-1.50)</td>
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<td>Cohort studies</td>
<td>7</td>
<td>0.79 (0.51-1.02)</td>
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<tr>
<td>Before-after studies</td>
<td>18</td>
<td>0.56 (0.34-0.81)</td>
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</table>

*Figure 5: Summary forest plot of the incidence ratios for studies investigating the effect of ASPs on antibiotic resistance, according to study characteristics. ICM = Infection control measure. ASP = Antibiotic stewardship programme.*
Antimicrobial Stewardship: Why Now?

• ASP is **NOT** a new concept in healthcare
• 25% reduction of outpatient antibiotic prescriptions in Canada since 1998, but little change over last decade
• 30-50% of antibiotic prescriptions unnecessary
• Increasing AMR
• Few new antimicrobials coming on the horizon
Decline of Antibiotics

Number of Approved Antibiotics

- Approved Antibiotics
Antimicrobial Resistance is a Public Health Threat

- AMR now: 700,000 (low estimate)
- AMR in 2050: 10 million
- Tetanus: 60,000
- Road traffic accidents: 1.2 million
- Cancer: 8.2 million
- Measles: 130,000
- Cholera: 100,000 - 120,000
- Diarrhoeal disease: 1.4 million
- Diabetes: 1.5 million
How do we stop the spread of resistance?

• “sand bags”
  
• Prevent the passage of the organism from person to person
  1. Sanitation
  2. Hand hygiene
  3. Infection Control principles and practice

• “stop the rain”
  
• Don’t enable the organism to grow:
  1. Restrict the antibiotic environment which gives the organism its survival advantage
  2. Use effective antimicrobial which evades the resistance

Appropriate use of antibiotics = Antimicrobial Stewardship
Antimicrobial Stewardship (ASP)

• How the appropriate use of antibiotics can maximize both their current effects and the chances of their being available for future generations
Myths about antibiotics

• More is better
  “broad spectrum superior to narrow spectrum”
  “longer duration superior to shorter”
  “finish the entire course”

• Individual prescribing has no impact on resistance

• “Better safe than sorry”
  • Improved diagnostics

• Antibiotics are safe
Association of Adverse Events With Antibiotic in Hospitalized Patients

Pranita D. Tamka, MD, MHS; Edina Avdik, PharmD, MBA; David X. Li, BS; Kathryn Dzintars, PharmD; Sara L. Cosgrove, MD, MS

**IMPORTANCE** Estimates of the incidence of overall antibiotic-associated adverse drug events (ADEs) in hospitalized patients are generally unavailable.

**RESULTS** In 1488 patients, the median age was 59 years (interquartile range, 49-69 years), and 758 (51%) participants were female. A total of 298 (20%) patients experienced at least 1 antibiotic-associated ADE. Furthermore, 56 (20%) non-clinically indicated antibiotic regimens were associated with an ADE, including 7 cases of *C difficile* infection. Every additional 10 days of antibiotic therapy conferred a 3% increased risk of an ADE. The most cardiac, and neurologic; and 90 days for the development of *Clostridium difficile* infection or incident multidrug-resistant organism infection, based on adjudication by 2 infectious diseases trained clinicians.

**RESULTS** In 1488 patients, the median age was 59 years (interquartile range, 49-69 years), and 758 (51%) participants were female. A total of 298 (20%) patients experienced at least 1 antibiotic-associated ADE. Furthermore, 56 (20%) non-clinically indicated antibiotic regimens were associated with an ADE, including 7 cases of *C difficile* infection. Every additional 10 days of antibiotic therapy conferred a 3% increased risk of an ADE. The most common ADEs were gastrointestinal, renal, and hematologic abnormalities, accounting for 78 (42%), 45 (24%), and 28 (15%) 30-day ADEs, respectively. Notable differences were identified between the incidence of ADEs associated with specific antibiotics.

**CONCLUSIONS AND RELEVANCE** Although antibiotics may play a critical role when used appropriately, our findings underscore the importance of judicious antibiotic prescribing to reduce the harm that can result from antibiotic-associated ADEs.
Goal of Antibiotic Therapy

- The right antimicrobial, dose and duration

- Goal: cure infection with minimal toxicity and minimal impact on selective pressure (i.e., resistance).

- **Inappropriate Use** leads to:
  - Adverse reactions (allergy, c.diff)
  - Antibiotic resistance and “super-infections”
  - Increased costs and LOS
Clostridium difficile

CLOSTRIDIUM DIFFICILE

THREAT LEVEL URGENT

250,000 INFECTIONS PER YEAR
14,000 DEATHS

$1,000,000,000,000 IN EXCESS MEDICAL COSTS PER YEAR
Antibiotics Cause Harm Beyond the Recipient

Residents of long-term care homes that use more antibiotics are more likely to experience antibiotic-related harm (including *C. difficile*, antibiotic-resistant organisms).\(^1\)

Patients on hospital wards that use more antibiotics are at higher risk of acquiring *C. difficile* infection, even when they haven't recently received antibiotics.\(^2\)

Receiving an antibiotic while hospitalized increases the risk that the next patient occupying the same bed will acquire *C. difficile*.\(^3\)

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Antimicrobial Stewardship is Needed in All Sectors

80% Animals

20% Humans

7% Hospital

93% Community

PHO Antimicrobial Stewardship Strategies for health care institutions


www.publichealthontario.ca/ASP

Intervention Type

- Formulary-related
- Structural/Process
- Clinical
- Prescribing Guidance
- Microbiology-related

Program Stage

- Early
- Intermediate
- Advanced
Ontario ASP Landscape Survey: Response Rate

Survey invitation sent (N=131)
Mental health, Ambulatory Care excluded

74% Response rate (n=97)

- Large Community: 45% (44)
- Small Community: 28% (27)
- CCC & Rehab: 11% (11)
- Acute Teaching: 15% (15)
Q: Do you currently have a formal ASP at your organization?

Almost all have or are building a formal Antimicrobial Stewardship Program.

Implementing 5% (5/97)

Yes 88% (85/97)

No 7% (7/97)

- Acute Teaching • 93% (14/15)
- Large Community • 93% (41/44)
- Small Community • 78% (21/27)
  • 15% in progress (4/27)
- CCC & Rehab • 82% (9/11)
  • 9% in progress (1/11)

Denominator = 97
ASP COMPARISON TOOL
## Comparison Table

<table>
<thead>
<tr>
<th>Hospital/Corporation Name</th>
<th>Dose Optimization</th>
<th>Scheduled reassessments</th>
<th>Targeted review of patients with CDR</th>
<th>Targeted review of redundant therapy</th>
<th>Therapeutic drug monitoring</th>
<th>De-escalation &amp; streamlining</th>
<th>Identification of bug-drug mismatch</th>
<th>Preventing treatment of non-infectious conditions</th>
<th>Prospective audit with intervention &amp; feedback</th>
<th>Targeted review of patients with bacteria/fungus</th>
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## ASP Strategies and Implementation Graph

- **Dose Optimization**: 8
- **Scheduled reassessments**: 6
- **Targeted review of patients with CDR**: 4
- **Targeted review of redundant therapy**: 6
- **Therapeutic drug monitoring**: 8
- **De-escalation & streamlining**: 4
- **Identification of bug-drug mismatch**: 2
- **Preventing treatment of non-infectious conditions**: 3
- **Prospective audit with intervention & feedback**: 8
- **Targeted review of patients with bacteria/fungus**: 2

Targeted review of patients with CDR:
- 63% (24 of 34) participating hospitals have implemented this strategy.
- 44% (4 of 9) selected hospitals have implemented this strategy.

Number of selected hospitals that implemented strategy.
Community Prescribing

2016-17

• 8,300,000 antibiotic Rx

• 25% of antimicrobial prescribing in Ontario is done by 2.2% of physicians

• Prescribing is a learned behavior. How do we target change?
Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial

Michael Hallsworth, Tim Chadborn, Anna Sallis, Michael Sanders, Daniel Berry, Felix Groaves, Lara Clements, Sally C Davies

Lancet 2016; 387: 1743-52

73,406 antibiotics dispensed
PHO’s Antimicrobial Stewardship Program (ASP) Goals:

Promote antimicrobial stewardship as part of an overall public health strategy to address AMR in Ontario.

Provide insights on the state of antibiotic stewardship and antibiotic use and in Ontario and identify opportunities to advance stewardship in Ontario.

Increase knowledge on what and how particular antimicrobial stewardship interventions should be implemented to advance stewardship in each sector.

Increase the implementation, scope and robustness of individual antimicrobial stewardship programs in Ontario.
Antimicrobial Stewardship is Everyone’s Role

**Prescriber**: assess benefits and risks of antibiotic therapy

**Patient**: question the need for antibiotics, understand when antibiotics are not necessary

**Policy maker**: facilitate antimicrobial stewardship in all sectors

**Public health**: advocate for antimicrobial stewardship and integrate with other approaches for maximal effect, provide data and expertise
What is changing?

• Accreditation Canada for ASP in acute care
• Trial of audit and feedback to LTC prescribers
• Acquire antibiotic use data in the community sector to inform a peer-comparison feedback intervention
• Federal Gov’t has new regulations limiting the importation of antimicrobials for animal use
  • Exclusion of antimicrobials for growth promotion
  • Antibiotics for infection treatment is still appropriate
  • What we call Infection Control, the animal sector calls Biosecurity
Why should ICPs care about ASP?

• It's all about patient safety

• The best way to treat an infection is to prevent it in the first place

• IPAC + ASP = AMR

• Stewardship programs can learn from the IPAC experience
  Working with lack of resources
  Influence without authority
  Multi-stakeholder collaboration
  Interface between the lab and the bedside
  Promoting behavior change
“The world is heading towards a post-antibiotic era in which common infections will once again kill...If current trends continue, sophisticated interventions, like organ transplantation, joint replacements, cancer chemotherapy and care of pre-term infants, will become more difficult or even too dangerous to undertake. This may even bring the end of modern medicine as we know it.”

- Margaret Chan, Director-General

World Health Organization
Thank you to Gary Garber and Brad Langford for contributing slides

Contact: asp@oahpp.ca
Kevin.schwartz@oahpp.ca

THANK YOU!

QUESTIONS?