AMR in Manitoba and Canada – What can we expect?

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Medical Officer of Health
Manitoba Public Health
OBJECTIVES

• Overview of the emerging threat AMR poses to medicine and society
• Snapshots of Manitoban and Canadian AMR
• Overview of Canadian and international initiatives
THE POST-ANTIBIOTIC ERA?
WHO AMR REPORT

ANTIMICROBIAL RESISTANCE
Global Report on surveillance 2014

What you need to know
WHO’s first global report on antimicrobial resistance, with a focus on antibiotic resistance, reveals that it is no longer a prediction for the future. Antibiotic resistance - when bacteria change and antibiotics fail - is happening right now, across the world.

The report is the most comprehensive picture to date, with data provided by 114 countries.
Looking at 7 common bacteria that cause serious diseases from bloodstream infections to gonorrhoea.
High levels of resistance found in all regions of the world.
Significant gaps exist in tracking of antibiotic resistance.

Over the last 30 years, no major new types of antibiotics have been developed.

Source: http://www.who.int/drugresistance/documents/surveillancereport/en/
INTERNATIONAL AMR PATTERNS

Available National Data* on Resistance for Nine Selected Bacteria/Antibacterial Drug Combinations, 2013

Number of requested bacteria/antibacterial medicine resistance combinations for which data was obtained:
- >5 \( (n=89) \)
- 2-5 \( (n=22) \)
- 1 \( (n=3) \)
- National data not available \( (n=15) \)
- No information obtained for this report, some centres participate in some ANSORP projects \( (n=2) \)
- No information obtained for this report, some centres participate in some RusNet projects \( (n=3) \)
- No information obtained for this report \( (n=60) \)

*National data means data obtained from official sources, but not that data necessarily are representative for the population or country as a whole.
Neisseria Gonorrhoeae

Detection of decreased susceptibility to 3rd generation cephalosporin and treatment failures up to 2010

*Note: cefixime > 0.25μg/L or ceftriaxone > 0.125μg/L. The definition of decreased susceptibility to third-generation cephalosporins differs across AMR testing methods. Countries are shaded where there has been any report of decreased susceptibility within their jurisdiction.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSIS)
World Health Organization
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Outpatient antimicrobial use (defined daily dosage (DDD) per 1,000 persons per day) reported in Canada and in 30 European countries

### Table 14: Total consumption for the top 10 antimicrobials* dispensed by community pharmacies (DDDs per 1,000 inhabitants) in Canada, 2007 to 2014

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<tr>
<td>Amoxicillin</td>
<td>1</td>
<td>1597.2</td>
<td>1624.1</td>
<td>1641.8</td>
<td>1691.4</td>
<td>1836.3</td>
<td>1768.9</td>
<td>1758.9</td>
<td>1843.5</td>
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<tr>
<td>Amoxicillin and enzyme inhibitor</td>
<td>4</td>
<td>244.5</td>
<td>262.0</td>
<td>271.6</td>
<td>239.0</td>
<td>314.7</td>
<td>333.9</td>
<td>368.5</td>
<td>405.8</td>
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<tr>
<td>Azithromycin</td>
<td>7</td>
<td>284.4</td>
<td>288.0</td>
<td>289.4</td>
<td>282.7</td>
<td>370.6</td>
<td>367.7</td>
<td>308.9</td>
<td>310.3</td>
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<tr>
<td>Cephalexin</td>
<td>6</td>
<td>342.6</td>
<td>348.6</td>
<td>337.4</td>
<td>330.0</td>
<td>354.1</td>
<td>358.7</td>
<td>368.9</td>
<td>371.1</td>
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<tr>
<td>Ciprofloxacin</td>
<td>5</td>
<td>439.6</td>
<td>442.8</td>
<td>425.2</td>
<td>434.4</td>
<td>444.1</td>
<td>428.2</td>
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<td>390.8</td>
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<td>Clarithromycin</td>
<td>2</td>
<td>982.5</td>
<td>997.6</td>
<td>1009.0</td>
<td>985.6</td>
<td>1028.8</td>
<td>965.6</td>
<td>830.6</td>
<td>743.0</td>
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<tr>
<td>Doxycycline</td>
<td>3</td>
<td>313.0</td>
<td>336.6</td>
<td>346.9</td>
<td>411.5</td>
<td>449.9</td>
<td>477.8</td>
<td>510.1</td>
<td>548.0</td>
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<tr>
<td>Minocycline</td>
<td>9</td>
<td>371.6</td>
<td>370.9</td>
<td>349.2</td>
<td>374.4</td>
<td>357.8</td>
<td>319.6</td>
<td>299.4</td>
<td>275.4</td>
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<tr>
<td>Nitrofurantoin</td>
<td>8</td>
<td>211.7</td>
<td>226.4</td>
<td>241.9</td>
<td>256.2</td>
<td>271.4</td>
<td>284.5</td>
<td>283.8</td>
<td>292.5</td>
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<tr>
<td>Sulfamethoxazole and trimethoprim</td>
<td>10</td>
<td>287.5</td>
<td>285.2</td>
<td>282.8</td>
<td>279.3</td>
<td>274.9</td>
<td>254.1</td>
<td>248.3</td>
<td>245.3</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>3477.4</strong></td>
<td><strong>5182.2</strong></td>
<td><strong>5195.2</strong></td>
<td><strong>5284.5</strong></td>
<td><strong>5702.6</strong></td>
<td><strong>5559</strong></td>
<td><strong>5383.2</strong></td>
<td><strong>5425.7</strong></td>
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</tbody>
</table>

* Ranked from greatest to least DDDs at the national level in 2014.

33%
### Prevalence of Common Resistance Isolated Genotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>N</th>
<th>% Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>391/1,850</td>
<td>21.1%</td>
</tr>
<tr>
<td>VRE</td>
<td>5/385</td>
<td>1.2%</td>
</tr>
<tr>
<td>ESBL <em>E. coli</em></td>
<td>123/2,965</td>
<td>4.1%</td>
</tr>
<tr>
<td>ESBL <em>K. pneumoniae</em></td>
<td>10/628</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

- Bacteriology of Top Urinary Organisms in Canadian ED’s – 61% *E. coli*
- 98% susceptible to Nitrofurantoin
- Bacteriology of Top Wound Organisms in Canadian ED’s – 42.1% *S. aureus* (MSSA)
- 98% susceptible to Doxy

MB STI RESISTANCE

• 354 clinical samples tested from 2012 to 2016
• 12 molecular strain types all resistant to azithromycin were found among 74 (21%) PCR-positive syphilis patients
• One patient was infected by two different strain types nine months apart

http://www.gov.mb.ca/health/publichealth/cdc/protocol/syphilis.pdf - NO AZITHRO USE

Source: Molecular typing and macrolide resistance of syphilis cases in Manitoba, Shuel M, et al. Sexually Transmitted Diseases, Publish Ahead of Print, DOI: 10.1097/OLQ.0000000000000734
AMR DEVELOPMENT

Antibiotic deployment


Sulfonamides  Penicillin  Chloramphenicol  Erythromycin  Vancomycin  Cephalosporins  Ampicillin  Methicillin  Tetracycline

Source: Nature Chemical Biology; 2007; 3: 541-548
EPIDEMIOLOGY OF AMR

Reasons for Inappropriate Prescribing

- Inadequate diagnosis, or lack of diagnostic facilities/resources
- Compliance with patients’ inappropriate demand or pressure to prescribe antibiotics
  - Patient satisfaction
- Fear of adverse outcomes, or litigation
- Influence from senior colleagues
- Lack of knowledge
  - Incorrect selection, dose, duration, and route of antimicrobial rx
- Financial gain/pressure from pharmaceutical industry
CONCLUSIONS

• Antimicrobial resistance is real and here in MB
• We are **ALL** responsible for addressing the causes and the solutions
• Addressing this requires participation from all stakeholders
• Can we lose our social license to practice if we ignore this issue?
Antimicrobial Stewardship
Improving Antimicrobial Prescribing
*(May the Forces Be with You...)*

Sergio Fanella MD, FRCPC, DTM&H
Assistant Professor & Program Director, Pediatric ID
University of Manitoba

*These are not the antibiotics you were looking for...*
Objectives

• Understand antimicrobial stewardship & rationale for ASPs

• Discuss aspects of ASPs relevant to the different settings

• Review the experience from an inpatient ASP at Children’s Hospital
What fruit helped save lives in WWII and change modern medicine?

- A. Watermelon
- B. Kiwi fruit
- C. Cantaloupe
- D. Spartan apples
- E. Hawaiian pineapples
Anne Miller, 90, First Patient Who Was Saved by Penicillin

Anne Sherae Miller, who made medical history as the first patient ever saved by penicillin, died on May 27 in Salisbury, Conn. She was 90.

In March 1942, Mrs. Miller was near death at New Haven Hospital suffering from a streptococcal infection, a common cause of death then. She had been hospitalized for a month, often delirious with her temperature spiking to nearly 107, while doctors tried everything available, including sulfas drugs, blood transfusions and surgery. All failed.

As she slipped in and out of consciousness, her desperate doctors obtained a tiny amount of what was still an obscure, experimental drug and injected her with it. Her hospital chart, now at the Smithsonian Institution, registered a sharp overnight drop in temperature; and by the next day she was no longer delirious and soon was eating full meals, one of her doctors reported.

Mrs. Miller’s life was saved, and so eventually were the lives of all those previously killed by infections of bacteria like streptococci, staphylococci.
In the News for the Wrong Reasons

The superbug that doctors have been dreading just reached the U.S.

https://www.washingtonpost.com/news/to-your-health/wp/2016/05/26/the-superbug-that-doctors-have-been-dreading-just-reached-the-u-s/?utm_term=.a6ce70aa33f0

Man, that’s going to take a HUGE wall...

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

AMR now
700,000
(low estimate)
Audience Question

- Antimicrobials are over-prescribed to children in Canada
  - A. Strongly agree
  - B. Agree
  - C. Neutral
  - D. Disagree
  - E. Strongly disagree
Q14 Overall, antibiotics are over-prescribed to children in Canada.
Answered: 74  Skipped: 2

- Strongly agree: ~91% Agree
- Agree: ~50% Agree
- Neutral: ~50% Agree
- Disagree: ~50% Agree
- Strongly disagree: ~50% Agree

Q15 Overall, antibiotics are over-prescribed to children at Children’s Hospital in Winnipeg.
Answered: 74  Skipped: 2

- Strongly agree: ~91% Agree
- Agree: ~50% Agree
- Neutral: ~50% Agree
- Disagree: ~50% Agree
- Strongly disagree: ~50% Agree
• A **system which optimizes the use of antimicrobial agents**

• Promotes **safety, quality of care**

• Apply to your setting (hospital vs. clinics)
Why ASPs?

• Inappropriate use of antimicrobials HARMS patients
  – “Antimicrobial chemotherapy”
• Collateral Damage
Why ASPs?

- **Clostridium difficile disease**
  - Increasing in hospitalized kids
  - 10X increase in community-onset
  - Hospital-onset C.diff infections:
    - ↑ risk of mortality OR 6.73 (3.77-12.02)
    - ↑ length of stay – 5.5 days (4.5-6.5 days)
    - ↑ hospital costs - $93K ($80-107K)

- **ADEs**
  - 20% of all pediatric ADE presenting to ER
  - TMP-SMX – 13 cases/100K admissions in 2013 (tripled)
ASP Strategies

Strong Recommendations

• Prospective-audit with feedback
• Pre-authorization
  – Aka ID approval required
• IV to oral conversion programs
• Interventions to ↓use of Abx associated with high risk of C. diff
• Dedicated PK monitoring program
Outcomes

• Need to measure **something**
• Process vs. Outcome metrics
• **Process Metrics**
  – health care service provided to, or on behalf of, a patient
  – E.g. guideline compliance, how Abx are used, DDD vs DOT vs LOT, costs
Outcomes

• **Outcome metric**
  - Health state of a patient resulting from health care
  - Reflect the cumulative impact of multiple processes of care
  - E.g. length of stay, mortality, ICU admission rates,
    • *C. diff* rates, adverse drug events
    • Antimicrobial resistance rates
A Pilot ASP at Children’s Hospital

- Grant from Child Health Advisory Committee (CHAC)
- 12 months (July 2013 – July 2014)
- 0.6 FTE pharmacist (Ms. Ashley Walus)
- Prospective Audit with Feedback
  - M/W/F
  - Elm/Oak/Pine/PICU
  - All systemic antimicrobials
- Note in chart when agreement

Affiliated with the University of Manitoba
Overall acceptance rate = 69%

Number of Recommendations

- D/C Unnecessary Therapy
- Narrow Coverage
- Optimize Dose
- Substitute Agent
- Consult ID
- D/C Duplicate Therapy
- Convert to PO
- Drug-Bug Mismatch
- D/C as Completed Course
- Broaden Coverage
- Convert to IV
- Other
### Table 1: Patient cases per ASP Shift

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<tr>
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<th>Elm</th>
<th>Oak</th>
<th>Pine</th>
<th>PICU</th>
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<tr>
<td><strong>Cases (#)</strong></td>
<td>6 (0 – 11)</td>
<td>6 (1 – 12)</td>
<td>6 (1 – 16)</td>
<td>4 (1 – 8)</td>
</tr>
<tr>
<td><strong>Time (mins)</strong></td>
<td>8 (0 – 30)</td>
<td>10 (1 – 30)</td>
<td>10 (1 – 30)</td>
<td>5 (0 – 30)</td>
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### Table 2: Median Length of Stay

<table>
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<tbody>
<tr>
<td><strong>P-value</strong></td>
<td>4.0</td>
<td>3.5</td>
<td>0.49</td>
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</table>
Ambulatory ABx

- Est. 50 million Abx Rx annually
  - ~20% of all visits
  - ~50% (24.6 million) received broad-spectrum (azithromycin)
  - 70% for respiratory conditions
- 23% for respiratory conditions not needing abx...
Choose wisely.

GET SMART
Know When Antibiotics Work
www.cdc.gov/getsma

Antibiotics aren't always the right tool for the job.

Antibiotics aren't effective in treating most colds, coughs or flu. Be careful - talk to your doctor about what you need, and what you don't. To learn more, visit choosingwiselynl.ca

WARNING: Antibiotics don't work for viruses like colds and the flu. Using them for viruses will NOT make you feel better or get back to work faster.

Antibiotics are strong medicines. Keep them that way. Prevent antibiotic resistance. Antibiotics don’t fight viruses – they fight bacteria. Using antibiotics for viruses can put you at risk of getting a bacterial infection that is resistant to antibiotic treatment. Talk to your healthcare provider before antibiotics. See www.cdc.gov/getsma or call 1-800-CDC-INFO to learn more.

Taking antibiotics for viral infections such as a cold, a cough, or the flu will NOT:
- Cure the infection
- Keep other people from catching it
- Help you feel better

Antibiotic Resistance Twitter Chats
November 18, 2014

Join @CDC_eHealth
3 pm EST
#SaveAbx

Join the 24 hour global chat #AntibioticDay

www.cdc.gov/getsma/week
Box. The Imbalance in Factors Related to Antibiotic Prescribing

Factors Driving Antibiotic Prescribing: Immediate and Emotionally Salient
- Belief that a patient wants antibiotics
- Perception that it is easier and quicker to prescribe antibiotics than explain why they are unnecessary
- Habit
- Worry about serious complications and "just to be safe" mentality

Factors Deterring Antibiotic Prescribing: More Remote and Less Emotionally Salient
- Risks of adverse reactions and drug interactions
- Recognizing the need for antibiotic stewardship
- Desire to deter low-value care and decrease unnecessary health care spending
- Prefer to follow guidelines
How do we tip the balance?
How about a little nudge?

NUDGE, NUDGE, SAY NO MORE?
Meeker D et al. *JAMA Inter Med* 2014;174(3);425

- 5 Los Angeles community clinics, adult patients
- Randomized to either:
  - Signed-commitment-poster in exam room x 12 weeks
  - vs. no poster in office
- Lay-person explanation to why using less Abx
- Baseline & intervention period Abx data analysis
- Patients with an acute respiratory infection (ARI) diagnosis
  - frame with one influenza season
- Looked at ARI Dx for which Abx inappropriate and appropriate
~20% ↓ Inappropriate Use

• MDs & NPs; in practice x 17.6 years

<table>
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<tr>
<th>Characteristic</th>
<th>Poster Condition</th>
<th>Control Condition</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Final Measurement</td>
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<tr>
<td>Inappropriate prescribing rate, % (95% CI)</td>
<td>43.5 (38.5 to 49.0)</td>
<td>33.7 (25.1 to 43.1)</td>
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<tr>
<td>Absolute percentage change, baseline to final</td>
<td>-9.8 (0.0 to -19.3)</td>
<td>9.9 (0.0 to 20.2)</td>
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<tr>
<td>measurement (95% CI)</td>
<td></td>
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<tr>
<td>Difference in differences between poster condition</td>
<td>-19.7 (-5.8 to -33.04)(^b)</td>
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<tr>
<td>and control (95% CI)</td>
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Abbreviation: ARI, acute respiratory infection.

\(^a\) Adjusted for demographic characteristics and insurance status.

\(^b\) \(P = .02\) for the difference.
Outpatient Audit & Feedback

- Network of 25 primary care pediatric practices
  - 9 control vs. 9 intervention groups
  - Common EMR
- Clinical education sessions q4 months + 1 year personalized, quarterly audit & feedback on Abx Rx’s
- Broad vs. narrow spectrum use
  - pneumonia; sinusitis; pharyngitis; “viral infection”

Gerber JS et al. JAMA 2013;309(22):2345-2352
Figure 2. Standardized Rates of Broad-Spectrum Antibiotic Prescribing at Acute Care Office Visits Over Time

$P = .01$

Control practices

Intervention practices
Durability & A Lasting Impression

Figure. Standardized Rates of Broad-Spectrum Antibiotic Prescribing Before, During, and After Audit and Feedback

- Pediatric primary care practices
- Control
- Intervention

JAMA December 17, 2014 Volume 312, Number 23
Pediatrician Perceptions

• Ignoring of reports; distrust
  – Didn’t believe them
  – Data integrity

• “Gaming” behaviour
  – Adding bacterial Dx codes during ARTI

• Liked idea of guidelines, just not following them...

• Parental pressure

• Perceptions of antibiotic overuse
  – It’s not me, it’s them...
Another Nudge in the Right Direction
Meeker D et al. JAMA 2016;315(6);562-70

• RCT in 47 clinics, ~250 MDs
• Rx rates for Abx-inappropriate visits
• Effect of 3 behavioral interventions
  – Suggested alternatives
  – Accountable justification
  – Peer comparison
• 0,1,2,or 3 of these
- Decreased in all groups
- **Significant only in accountability + peer comparison group**

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**Figure 2. Adjusted Rates of Antibiotic Prescribing at Primary Care Office Visits for Antibiotic-Inappropriate Acute Respiratory Tract Infections Over Time**

A. Accountable justification

B. Peer comparison

C. Suggested alternatives

Prescribing rates for each intervention are marginal predictions from hierarchical regression models of intervention effects, adjusted for concurrent exposure to other interventions and clinician and practice random effects. Error bars indicate 95% CIs. Model coefficients are available in eTable 3 in Supplement 2.
<table>
<thead>
<tr>
<th>Communication strategy</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Explanation for why antibiotics are not needed | “This is a nasty cold, so antibiotics won’t make you better faster.”
“The strep test is negative, meaning your sore throat is caused by a virus, and antibiotics won’t help.”
“You have a chest cold, and antibiotics won’t help.”
**Tip for clinicians:** Patients are less likely to expect antibiotics for “chest colds” than for “bronchitis.”
*Always combine explanations for why antibiotics are not needed with positive treatment recommendations. Patients are willing to hear that antibiotics are not needed if the message is combined with how to help them feel better.*

| Positive treatment recommendations | “Taking ibuprofen and drinking plenty of fluids will help you feel better.”
“Honey can actually soothe your child’s cough and help her sleep better.” |

| Contingency plan | “If you are not better in three or four days, call or come back and we can reassess the need for antibiotics then.”
“If your child is still sick in a week or if he develops a fever, come back and see me.” |

| Delayed antibiotic prescriptions | “Your child has an ear infection that will likely clear up on its own. If the ear still hurts in two days or gets worse, call or come back and we will recheck the ears.”
“Your child has an ear infection that will likely clear up on its own. Just in case it doesn’t, here is an antibiotic prescription. Fill this prescription in two days if the ear still hurts, or earlier if your child gets worse. Feel free to call me with any questions.”
**Tip for clinicians:** When using delayed prescriptions, write an expiration date on the prescription (e.g., five to 10 days in the future) so that the prescription can be filled only during the watchful waiting period and not a few months later.” |
Conclusions

• Antimicrobial “chemotherapy”
  – misuse = harm
• ASPs are successful in lowering inappropriate Abx use safely
• Tailor an ASP to your needs
  – Low-hanging fruit
• A blend of:
  – Education
  – Behavioural economic techniques
  – Communication Strategies
• May need a few nudges...