What is the antimicrobial consumption as expressed in DDD (defined daily dose) per 1000 patient days for each type of patient sector/unit/common condition?

- Team name: Manitoba Primary Care Research Network
- Team members: Alexander Singer, William Peeler, Sylvia Froese, Brenden Dufault

Describing the Data and Analysis

- **Data Custodian Organization(s) and data sources**: Manitoba Primary Care Research Network – MaPCReN

- **List of Datasets Used (e.g. names of database and/or data origins)**: The MaPRCeN is composed of de-identified primary care data collected from participating primary care clinics. The repository is managed in partnership with the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). The database is located at the Queen's University High Performance Computing lab.

- **Exclusions**: Patients who opted out of data collection in the MaPCReN or were deceased.

- **Nature and Size of Cohort (e.g. geographic area covered, number of patients included)**: MaPCReN currently collects Electronic Medical Record Data from over 220 sentinels (primary care practices) from 40 sites (clinics) participating in the Winnipeg and Southern and Northern Manitoba Health Regions. This represents data from approximately 220,000 patients. Clinics are recruited to participate in MaPCReN directly by the Network Director and represent a diversity of primary care providers including Family Physicians and Nurse Practitioners in both Fee-for-Service and Salary models. The services offered at the primary care clinics include but are not limited to same day access, inter-professional team care, social services and specialty medical care.
  The Research Ethics Board Approval (REB) at the University of Manitoba has granted permission for all data collected from EMRs related to MaPCReN's work in building this repository. A second REB approval has been obtained related to the ongoing study which involves the antibiotic stewardship in primary care.

- **Data timeframe**: June 30, 2013 – June 30, 2015

- **Please provide a brief summary of the analysis methodology:**

  The analysis was conducted for 2 distinct types of diagnosis and the related linked antibiotic prescriptions, classified according to types of likely infection. Group 1 considered the appropriateness of antibiotic prescribing of conditions where the diagnosis was likely bacterial and therefore antibiotics are appropriate. Group 2 considered prescriptions in diagnosis where prescribing any antibiotic is considered not appropriate because the linked infection was likely

viral. *Appendix A describes the complete methodology and analysis in more complete detail then what is summarized here.*

We considered the defined daily dose for antibiotic prescribing related to the following conditions:

- Group 1 - "likely" diagnosis assigned based on the encounter/billing diagnosis related to each prescription if there is one available on the same day of the prescription or within 14 days of the prescription being issued. If there are two visits within 14 days of the prescription, the one nearest to the antibiotic prescription date was considered for the following diagnosis.
    - UTI – 599, 595.0
    - Pharyngitis – 462
    - Skin/soft tissue infections – 792
    - Cellulitis - 628, 681
    - Pneumonia - 486, 482.8
- Group 2 – comprised of diagnosis that were likely to be viral. P*lease see appendix A for complete definition and exclusions designed to eliminate the presence of chronic infections and immunosuppression.*
    - Acute mild-to-moderate sinusitis – acute sinusitis - 461
    - Upper respiratory tract infection - 465
    - bronchitis - 466
    - acute rhinitis - 460
    - nasopharyngitis - 477
    - influenza - 488/487

The above categories as defined by days of antibiotic prescription in the appropriate and inappropriate group. Please see Appendix A for a complete definition of how "appropriateness" of the prescription was determined based on the Infectious Diseases Society of America evidence based guidelines.

Describing the Findings

- Numerator and Denominator (as specified in the question definition).

DIAGNOSIS	**TOTAL DDD/1000 OF ANY ANTIBIOTIC BY CONDITION**
Group 1	
Pharyngitis	1.302
Pneumonia	0.876
UTI	8.936
Cellulitis	0.535
Skin/Soft Tissue	1.492
Group 2	
Influenza	0.356
Allergic Rhinitis	0.531

Acute Bronchitis	4.805
Acute Upper Respiratory Tract Infection	10.415
Acute Sinusitis	6.278
Acute Nasopharygitis/Common Cold	0.096
Otitis Media	8.784

- State the key statistics from your analysis.

For diagnosis likely to be caused by bacteria (Group 1) and based on our definition of "inappropriate prescription", 30% antibiotics in this sample were not prescribed in an ideal manner. When these antibiotics were used inappropriately 52% of the time the incorrect number of days was prescribed based on evidence based recommendations. There were 1293 unique prescriptions considered relating to 13,141 total days of antibiotic use.

In Group 2 where the 55,004 occurrences of the relevant diagnosis that were likely to be viral. A total of 5.5% of the time we observed an antibiotic associated with the diagnosis. This represented 3014 potentially inappropriate prescriptions relating to 31,265 total days of antibiotic use.

- Please also provide a brief summary of the findings including any key limitations or interpretation issues (may also include figures/tables).

The purpose of this our study is to develop interventions to target potentially inappropriate prescribing in primary care settings rather than simply track overall usage. Our key finding is that antibiotic stewardship interventions to improve prescribing in primary care are urgently required.

The table below demonstrates the DDD per each antibiotic based on ATC code for the Group 1 diagnoses. We have demonstrated DDD per each prescription and diagnosis and sub-classified as to whether the DDD in each category was "appropriate" or "inappropriate" based on our evidence based algorithm which considered the appropriate number of days prescribed and the ideal antibiotic choice. We have also included the DDD/1000 patient days.

DX CODE	RX CODE	APPROPRIATE?	DDD PER ABX	DDD/1000
729	J01AA02	Rx incorrect	273	0.273
600	J01AA07	Rx incorrect	35	0.035
730	J01AA08	Rx incorrect	58	0.058
599	J01CA01	Rx incorrect	7	0.007
730	J01CA04	Rx correct, duration correct	595	0.595
600	J01CA04	Rx incorrect	1128	1.128
599	J01CE02	Rx incorrect	108	0.108
462	J01CE09	Rx correct, duration correct	130	0.13
599	J01CE09	Rx incorrect	47	0.047

730	J01CF02	Rx correct, duration correct	19	0.019
599	J01CF02	Rx incorrect	31	0.031
600	J01CR02	Rx correct, duration incorrect	102	0.102
730	J01CR02	Rx incorrect	115	0.115
730	J01DB01	Rx correct, duration correct	289	0.289
486	J01DB01	Rx incorrect	725	0.725
599	J01DC02	Rx correct, duration correct	14	0.014
730	J01DC02	Rx incorrect	222	0.222
599	J01DC10	Rx correct, duration correct	10	0.01
486	J01DC10	Rx incorrect	10	0.01
599	J01EE01	Rx correct, duration correct	324	0.324
730	J01EE01	Rx incorrect	1353	1.353
599	J01FA01	Rx incorrect	10	0.01
730	J01FA01	Rx incorrect	10	0.01
486	J01FA09	Rx correct, duration correct	160	0.16
486	J01FA09	Rx correct, duration incorrect	58	0.058
730	J01FA09	Rx incorrect	146	0.146
486	J01FA10	Rx correct, duration incorrect	129	0.129
730	J01FA10	Rx incorrect	27	0.027
486	J01FF01	Rx incorrect	85	0.085
600	J01MA02	Rx correct, duration incorrect	2165	2.165
730	J01MA02	Rx incorrect	1021	1.021
599	J01MA06	Rx correct, duration correct	98	0.098
600	J01MA06	Rx correct, duration incorrect	299	0.299
599	J01MA12	Rx correct, duration correct	5	0.005
600	J01MA12	Rx correct, duration incorrect	90	0.09
730	J01MA12	Rx incorrect	217	0.217
483	J01MA14	Rx incorrect	20	0.02
486	J01MA14	Rx incorrect	25	0.025
729	J01XD01	Rx incorrect	21	0.021
600	J01XE01	Rx correct, duration correct	271	0.271
730	J01XE01	Rx incorrect	2689	2.689

The key limitation to our methodology is that we cannot be absolutely certain that our prescription and diagnosis pairs are always correct. We may also have under-captured the true number of occurrences in the case where a different diagnosis was entered in the bill or problem list. It is possible that a patient could present with multiple problems and in Manitoba only 1 diagnosis is entered per visit. So there are likely many prescriptions given that were not captured by this methodology as the associated diagnosis was unknown. Our methodology also assumed that the diagnosis used in the bill or encounter table was correct. This could have led to underreporting in

Group 2 as providers would be unlikely to enter a diagnosis for a likely viral condition if they were prescribing an antibiotic at the visit.

To capture a complete understanding of antibiotic consumption one would need to consider all prescriptions given, but that would limit the ability to know why the prescription was written using primary care EMR data. In order to do this more comprehensively more refined tools for natural language processing need to be developed to allow for more granular understanding of the rationale for the prescribing patterns. We also assumed that the number of days prescribed was the DDD. For the antibiotics in this study the range for DDD is the typical clinical usage for these medications but we did not perform a validation to verify that this was true for all prescriptions. It is possible in some cases that the WHO specified DDD was greater or less than that prescribed although clinically we used the judgement of the medical provider as equivalent to this administrative definition. As well, we cannot ascertain patient adherence from this data. It is possible that patients did not take the medications as prescribed so our data is most suited to describe prescriber patterns as opposed to the exact amounts of patient consumption which would require a different methodology.

- Provide any additional analysis or insight that goes beyond what was asked in the question.
  - ✓ Useful for earning extra ballot in Qualifying Answer Incentive Draw through a "special added value" designation from judges.

Our analysis to identify factors that affected inappropriate antibiotic prescribing uses multilevel regression modeling using SAS to determine which patient or provider factors lead to "inappropriate" patterns. The full analysis is ongoing and currently being refined. The following tables demonstrates the potentially statistically significant factors and associated p –values for Group 1 (prescriptions for diagnosis with likely bacterial cause).

Group 1 - Type III Tests of Fixed Effects

Effect	P-value
Patient Sex	0.0046
Patient Age	0.0100
Patient Co-morbidities	0.1637
Patient Visits	0.0002
Provider Age	0.0558
Provider Practice size	0.2230
International Medical Graduates	0.1014
Practice location	0.4290

Thus far, in Group 2 (diagnosis likely to be viral) none of the fixed effects shown above have been found to lead to statistically significant difference in likelihood of "inappropriate" prescribing among primary care providers or patient characteristics.

The following tables summarize the effects of the patient and provider characteristics in the Multi-level Logistic Regression Model for Group 1:

Patient Gender - Differences of Sex Least Squares Means				
Sex	**_Sex**	**Odds Ratio**	**Lower Confidence Limit for Odds Ratio**	**Upper Confidence Limit for Odds Ratio**
FEMALE	MALE	0.617	0.442	0.862

Differences of Patient Age			
Patient Age	**Odds Ratio**	**Lower Confidence Limit for Odds Ratio**	**Upper Confidence Limit for Odds Ratio**
30 & Younger	2.013	1.305	3.105
30 & Younger	1.776	1.150	2.741
30 & Younger	1.830	1.094	3.061
31 – 50	0.882	0.575	1.355
31 – 50	0.909	0.562	1.472
51 – 70	1.031	0.683	1.556

Patient Visits, Provider age, Comorbidity counts and Patients per Provider			
Label	**Odds Ratio**	**Lower Confidence Interval**	**Upper Confidence Interval**
per 5 unit increase in TOTAL PATIENT VISITS	1.1090	1.0498	1.1716
per 5 year increase in Provider AGE	0.9009	0.8094	1.0026
per 1 unit increase in DISEASE COUNT	0.8950	0.7656	1.0463
per 100 unit increase in PATIENT COUNT	1.0330	0.9804	1.0883

Differences in School of Graduation				
MD from Canadian School	**MD from Canadian School**	**Odds Ratio**	**Lower Confidence Limit for Odds Ratio**	**Upper Confidence Limit for Odds Ratio**
0	1	1.448	0.930	2.255

Differences of Provider Geography				
Provider Geography	**Provider Geography**	**Odds Ratio**	**Lower Confidence Limit for Odds Ratio**	**Upper Confidence Limit for Odds Ratio**
Inner City	Rural	1.767	0.777	4.015
Inner City	Small Town	1.768	0.875	3.573
Inner City	Urban / Suburban	1.427	0.647	3.147
Rural	Small Town	1.001	0.569	1.760
Rural	Urban / Suburban	0.808	0.393	1.659
Small Town	Urban / Suburban	0.807	0.454	1.434

- Describe the implications of this analysis for policy in no more than a few sentences.

The implication is that this is the first large scale study in primary care that assess the overall patterns of potentially inappropriate antibiotic prescribing. It not only establishes a baseline for quality improvement initiatives but is foundational to developing evidence informed targeted interventions to address antibiotic stewardship in primary care.
When completed, this study will lay the groundwork for further antibiotic stewardship programs in primary care which desperately needed to curtail the overuse of antibiotics in the setting where most are dispensed.

Appendix A – Analysis Plan for complete study with full inclusion/exclusion criteria and study design.

In order to answer these questions we will extract prescription data from the preceding 2 years in the 2015 Q2 MaPCReN repository for all antibiotics starting with ATC code J01:

Group 1 – Bacterial Infections

We will assign a "likely" diagnosis based on the encounter/billing table to each prescription if there is one available on the same day of the prescription or within 14 days of the prescription being issued. If there are two visits within 14 days of the prescription, the one nearest to the antibiotic prescription date will be considered.
We will consider the following diagnosis for analysis at this phase:

- UTI – 599, 595.0
- Pharyngitis – 462
- Skin/soft tissue infections – 792
- Cellulitis - 628, 681
- Pneumonia 486, 482.8

Prescriptions falling outside of evidence informed guidelines (IDSA) will be considered "inappropriate" and those within these guideline based standards will be considered "appropriate".
We will define the prescription as "appropriate" or "inappropriate" based on the following table

Diagnosis	**ICD9 code**	**Duration (in days)**	**Antibiotics:**	**ATC code**
Adult UTI	599*	3-5	TMP-SMX/septra	J01EE
	595.0		Ciprofloxacin	J01MA
			Fosfomycin	J01XX01
			Cephalexin	J01DB01
			Cefixime	J01DD08
			Amoxicillin-clavulanate	J01CR02
			Nitrofurantoin	J01XE
Pediatric UTI (under 16)	599*, 595.0	7-14	TMP-SMX/septra	J01EE
			Cephalexin	J01DB01
			Cefixime	J01DD08
			Cefprozil	J01DC10
			Cefuroxime	J01DC02
Pharyngitis	462	10	Penicillin	J01CE*
		10	Amoxicillin	J01CA04
With documented penicillin/beta lactam allergy*********		10	*Cephalexin*	*J01DB01*
		10	*Clindamycin*	*J01FF01*
		5	*Azithromycin*	*J01FA10*

		10	*Clarithromycin*	*J01FA9*
Soft tissue infection	729			
Cellulitis	628*,681*	5-7	Penicillin	J01CE*
			Amoxicillin	J01CA04
			Cloxacillin	J01CF*
			Cephalexin	J01DB01
			Clindamycin	J01FF01
Pneumonia (under 16)	486	7-10	Penicillin	J01CE*
			Amoxicillin	J01CA04
Adult Pneumonia	486, 482.8	7	Penicillin	J01CE*
		7	Amoxicillin	J01CA04
		5	Azithromycin	J01FA10
		10	Clarithromycin	J01FA9

We will be able to describe the patient and physician factors for each prescription and also for each physician practice we will create a table that describes the number of inappropriate and compared to the total prescriptions for each diagnosis.
See the example tables below:

Prescription Table:

Prescription (Antibiotic)	Diagnosis	Patient characteristics (multiple)	Prescriber Characteristics (multiple)	Inappropriate (Y/N)	Appropriate (Y/N)

Prescriber Table:

Sentinel #	Antibiotic	Practice Characteristics (Multiple)	% Inappropriate prescriptions	% Appropriate prescriptions	Total # of prescriptions			

Group 2 – Viral Infections

Antibiotics should not be prescribed for conditions that are usually viral. This analysis will attempt to gather a single point in time analysis (prescriptions over 2 year period) during which prescriptions were given in "inappropriately" for viral conditions. The following describes how these "inappropriate" prescriptions will be assigned for three common conditions; acute/moderate sinusitis, upper respiratory tract infections and ottits media in children.

1) Acute mild-to-moderate sinusitis - unless symptoms last for seven or more days, or symptoms worsen after initial clinical improvement *and* 2) Upper respiratory tract infections, influenza-like illness and bronchitis in the absence of significant risk factors for pneumonia.

- Visits billed with ICD-9 code starting with a code for acute sinusitis "461" or upper respiratory tract infection "465" or bronchitis "466" or acute rhinitis "460" or nasopharyngitis "477" or influenza "488/487"
- And a prescription for antibiotic using any ATC codes for "antimicrobials" (starting with J01) within 6 days.
- Exclude prescriptions linked to visit where a visit billed for sinusitis exists 7-21 days previously (to exclude chronic sinusitis).
- Exclude patients with Asthma, Bronchiectasis, Cystic Fibrosis or COPD as these can be considered high risk co-morbidities. These conditions will be defined by validated CPCSSN case definitions or presence in health condition (problem list) table.
- *Eligible Population (denominator) = total visit billed with ICD-9 code starting with a code for acute sinusitis "461" or upper respiratory tract infection "465" or bronchitis "466" or acute rhinitis "460" or nasopharyngitis "477" or influenza "488/487 not receiving a prescription for antibiotic.*

3) Otitis media in children:

- Ages 2-12 years with billing code for otitis media and prescription for antibiotic within 5 days of the visit
- Exclude prescriptions linked to visit where a visit billed for otitis media exists 5-14 days previously (381, 382)
- *Eligible Population = patients ages 2-12 years with billing code for otitis media not receiving a prescription for antibiotic*

Analysis

Upon assigning whether the prescription was appropriate or not, we intend on conducting a multilevel regression analysis to determine which patient or provider factors lead to "inappropriate" patterns. Of note some of the co-morbidities may require clinical judgement and therefore the prescribing may be reasonable based on the patient status. However, if provider factors are strong predictors of prescribing patters then interventions to address this may be able to be created.

We will consider all patients in a practice for which there are at least 2 years of data for and at least 1 office visit during that time. The data set we will use will be a SAS database created including the defined fields below from the MaPCReN 2015 Q2 Primary Care extract. We will consider data extracted from June 30, 2015 – June 30, 2013. Exclusions will include patients who have opted out of data collection, have more than one or no provider assigned.

The following is a list of the patient factors we will consider as independent variables:

- Co-morbid conditions (categorical) - defined further below.
    - None, 1-2, Greater than 3

- Age (categorical)
    - Pediatric (0-12), Young Adult (13-18), Adult/Elderly (19-90 in 10 year intervals)
- Gender (categorical)
    - Male, Female, Unknown or undefined
- # of visits per/year (categorical)
    - Rare (1-2), regular (3-9), frequent (>10)
- Socio-economic status based on postal code (categorical)
    - Based in income quintile (using MCHP algorithm)

The following are the co-morbid conditions that will be considered based on ICD-9 code in the problem list/health condition table. All are in the form of ICD9 code and should include 4,5 digit codes with more detailed descriptions:

- Asthma: 493
- Immunodeficiency: 279
- HIV: 042
- HTLV (similar virus to HIV): 079.53
- Atopic Dermatitis: 691
- Cystic Fibrosis: 277.0
- Diabetes 250 and COPD 496. *If there are any that flag in the problem list but not via case definition it might be worth a more detailed search.*

We will also consider the presence of one or more of the validated CPCSSN case definitions diagnosis which include:

- Diabetes
- Hypertension
- COPD
- Osteoporosis
- Depression
- Dementia
- Parkinson's Disease
- Epilepsy

The following is a list of the clinician factors we will consider as independent variables:

- Practice size (categorical)
    - Small (<600), Medium (600-1000), Large (>1000)
- Country of Graduation (categorical)
    - Canada, IMG
- Age of Provider (categorical)
    - <35, 35-54, >55
- Practitioner Type (categorical)
    - Family physician, nurse practitioner
- Practice Location (categorical)
    - Urban, rural, remote
- Funding Mode (categorical)
    - Salaried, Fee for Service
- Years using EMR (categorical)

- Less than 4 years, greater than 4 years