Measuring antimicrobial consumption

Guillaume Béraud

Université Laval, Canada

October 5th, 2017

Protecting antimicrobial

- Antimicrobial are mandatory tools for modern medicine (*try to perform a transplantation without antibiotics . . .*)
- Antimicrobials are excessively prescribed, which results in a rise of antimicrobial resistance, and less effective antimicrobials.
- Excessive prescription and antimicrobial resistance are not fatality, and can be tackled

According to WHO (Fact sheets, Sept. 2016)

- Antimicrobial resistance (AMR) threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi.
- AMR is an increasingly serious threat to global public health that requires action across all government sectors and society.
- Without effective antibiotics, the success of major surgery and cancer chemotherapy would be compromised.

World Health Organization

According to WHO (Fact sheets, Sept. 2016)

- The cost of health care for patients with resistant infections is higher than care for patients with non-resistant infections due to longer duration of illness, additional tests and use of more expensive drugs.
- Globally, 480 000 people develop multi-drug resistant TB each year, and drug resistance is starting to complicate the fight against HIV and malaria, as well.

World Health Organization

Antimicrobial resistance results from antimicrobial consumption

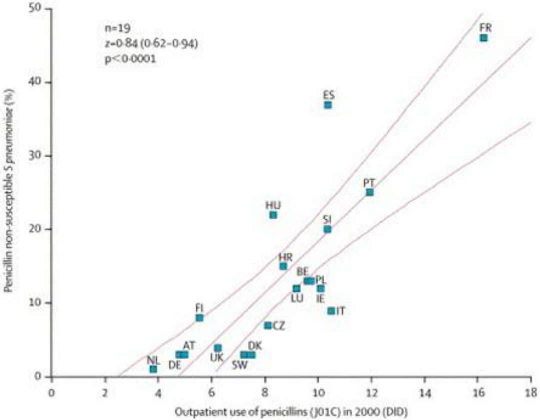


Figure – Goossens et al, Lancet 2005

And a decrease in antimicrobial consumption will result antimicrobial resistance

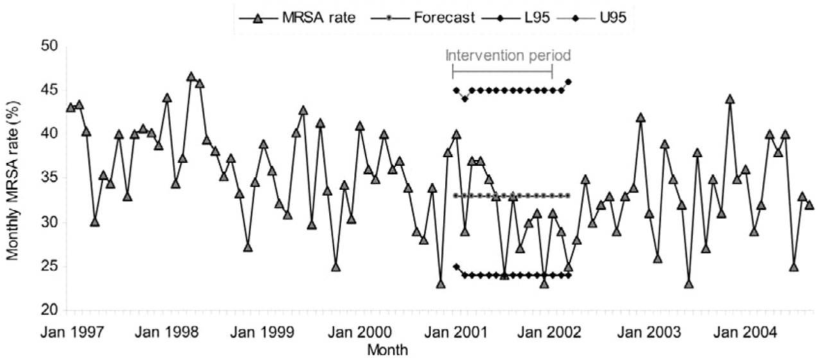
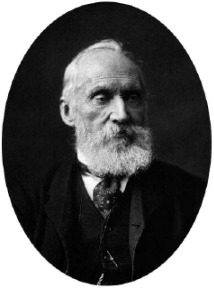


Figure – Charbonneau et al, CID 2006

To measure is to know



"If you cannot measure it, you cannot improve it"

——William Thomson

To model and to predict

Bruyndonckx et al linked resistance to penicillin in S. pneumoniae to consumption

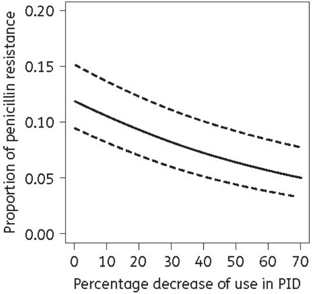


Figure – Bruyndonckx et al, JAC 2015.

What to measure

Antiinfectives

- Antibacterials
- Antifungals
- Antimycobacterials
- Antivirals

For

- Systemic use
- Local use

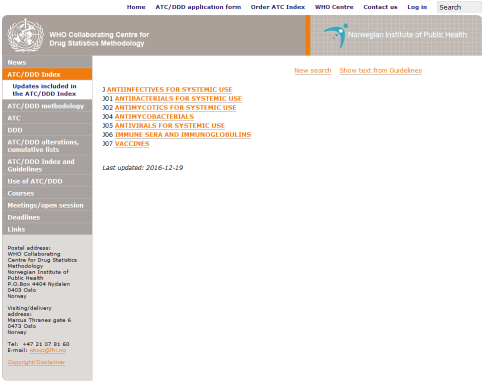
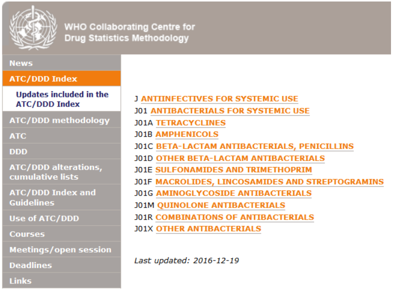


Figure – ATC stands for Anatomical Therapeutic Chemical

But a pharmacist classification . . . not straightforward !


WHO Collaborating Centre for Drug Statistics Methodology

News
ATC/DDD Index
Updates included in the ATC/DDD Index
ATC/DDD methodology
ATC
DDD
ATC/DDD alterations, cumulative lists
ATC/DDD Index and Guidelines
Use of ATC/DDD
Courses
Meetings/open session
Deadlines
Links

J ANTIINFECTIVES FOR SYSTEMIC USE
J01 ANTIBACTERIALS FOR SYSTEMIC USE
J01A TETRACYCLINES
J01B AMPHENICOLS
J01C BETA-LACTAM ANTIBACTERIALS, PENICILLINS
J01D OTHER BETA-LACTAM ANTIBACTERIALS
J01E SULFONAMIDES AND TRIMETHOPRIM
J01F MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
J01G AMINOGLYCOSIDE ANTIBACTERIALS
J01M QUINOLONE ANTIBACTERIALS
J01R COMBINATIONS OF ANTIBACTERIALS
J01X OTHER ANTIBACTERIALS

Last updated: 2016-12-19

- J01C Beta-lactam antibacterials, penicillins
  - aminopenicillins
  - ureidopenicillins
- J01D Other Beta-lactams
  - cephalosporins
  - carbapenems

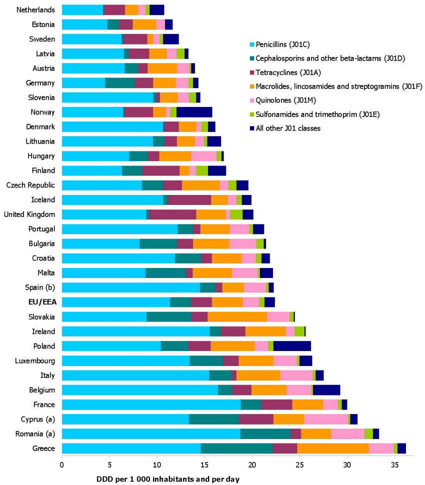


Figure – Consumption of antibiotics for systemic use in the community by antibiotic group, EU/EEA countries, 2015

How should we measure

Multiple methods

- Daily doses/1000 inhabitants/day (outpatient)
- Packages/1000 inhabitants/day (outpatient)
- Daily doses/100 hospital days (inpatients)
- Daily doses/100 cases (inpatients)

How should we measure

Multiple definitions and indicators

- DDD (Defined Daily Dose) : Assumed average maintenance dose per day for a drug used for its main indication in adults. (`www.whocc.no`). *Unrealistic (overestimation) but useful for international comparisons.*
- PDD (Prescribed Daily dose) : *Preferable ! ! !*
- RDD (Recommended Daily Dose) (`www.antiinfektiva-surveillance.de`) : *The German touch : Realistic but very "local".*

Table 1
Drugs most commonly used in the study hospital with differences in the definition of daily doses for antimicrobial agents as defined in the WHO/ATC index version 2007 and according to consensus practice guidelines of the university hospital of Freiburg.

Drug class/group	Drug	DDD (g)	RDD (g)
Narrow-spectrum betalactams	Penicillin G	3.6	12g
	Ampicillin	2	15
	Amoxicillin po	1	2.25
	Flucloxacillin	2	8
	Flucloxacillin po	2	3
	Penicillin V po	2	1.88
Intermediate-spectrum betalactams	Amoxicillin/clavulanic acid	3[a]	6
	Amoxicillin/clavulanic acid po	1[a]	1.75
	Cefaclor po	1	1.5
	Cefuroxim	3	4.5
	Cefuroxim-Axetil po	0.5	1
Broad-spectrum betalactams	Cefotaxim	4	6
	Ceftazidim	4	6
	Cefepim	2	6
	Piperacillin	14	12
	Piperacillin + tazobactam	14[a]	12
	Meropenem	2	3
Fluoroquionolones	Ciprofloxacin	0.5	0.8
	Ciprofloxacin po	1	1.5
Macrolides/clindamycin	Clarithromycin po	0.5	1
	Clarithromycin iv	1	1
	Clindamycin po	1.2	1.8
	Clindamycin iv	1.8	1.8
Aminoglycosides	Gentamicin	0.24	0.32
	Netilmicin	0.35	0.45
	Tobramycin	0.24	0.32
	Amikacin	1	1.5

Figure – From de With et al JAC 2009

Formulas

$$DDD = \frac{\text{Number of Units} \times \text{Amount of drug per unit}}{DDD \text{ of the drug}}$$

in general we express hospital consumption as a use density :

$$DDD/100 \text{ hospital-days} = \frac{\text{number of daily doses} \times 100}{\text{number of care days}}$$

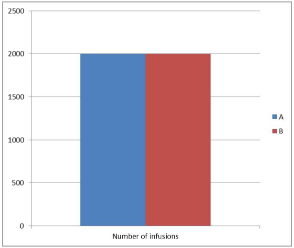
as only use density allows comparisons

Practical exercice

Let's compare 2 hospitals and their respective antibiotic consumption

- Hospital A : 2000 infusions of Cefotaxim (2 g per infusion), 60000 care days
- Hospital B : 2000 infusions of Piperacillin-Tazobactam (4 g per infusion), 30000 care days

Never compare infusions' number

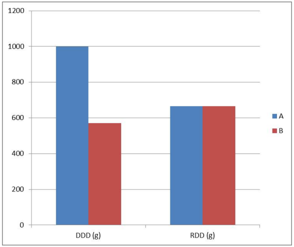


	Cefotaxim IV (hosp. A)	Pip-Taz IV (Hosp. B)
DDD	4g	14g
RDD	6g	12g
number of DDD		
number of RDD		
DDD/100		
RDD/100		

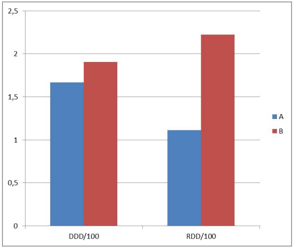
Let's do some math

$$DDD \text{ for Cefotaxime} = \frac{2000 \text{ infusions} \times 2g}{4g \text{ DDD of the drug}}$$

$$RDD \text{ for Cefotaxime} = \frac{2000 \text{ infusions} \times 2g}{6g \text{ RDD of the drug}}$$



	Cefotaxim IV (hosp. A)	Pip-Taz IV (Hosp. B)
DDD	4g	14g
RDD	6g	12g
number of DDD	1000	571
number of RDD	667	667
DDD/100		
RDD/100		



	Cefotaxim IV (hosp. A)	Pip-Taz IV (Hosp. B)
DDD	4g	14g
RDD	6g	12g
number of DDD	1000	571
number of RDD	667	667
DDD/100	1.7	1.9
RDD/100	1.1	2.2

- Antibiotic consumption 2006→2011 [1]
- 22 Norwegian hospitals
- DDD vs. hospital adjusted DDD (⇔RDD)

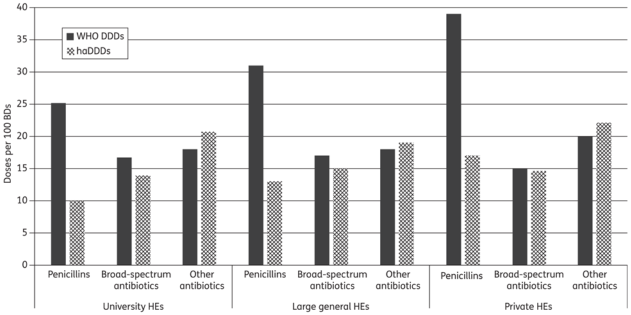


Figure – WHO defined daily doses versus hospital-adjusted defined daily doses : impact on results of antibiotic use surveillance

1. Haug et al JAC 2013

Table 3. Ranking[a] of the utilization of 24 antibiotics[b] in 22 Norwegian HEs; rankings based on both WHO DDDs and haDDDs

		Ranking order																
Antibiotics		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Benzylpenicillin/phenoxymethylpenicillin	WHO DDDs	22	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	haDDDs	8	5	3	5	1	—	—	—	—	—	—	—	—	—	—	—	—
Metronidazole	WHO DDDs	—	—	1	3	7	4	5	1	—	—	1	—	—	—	—	—	—
	haDDDs	8	9	2	1	1	—	—	—	1	—	—	—	—	—	—	—	—

Figure – Ranking of the utilization of 24 antibiotics in 22 Norwegian hospitals ; rankings based on both WHO DDDs and haDDDs

DDD vs. RDD

RDD provide

- a more realistic image of antimicrobial consumption.
- a less distorted inter-hospital comparison
- BUT, require similar recommendations
- Provide both !

PDD : Truly prescribed daily dose

- Point prevalence survey in a large German university hospital : PDD vs. DDD [2]
- *Of the 1,754 PDDs, 625 were matching DDD dose definitions (36%), and 1,024 (58%) were matching RDD dose definitions ($p < 0.01$)*
- *Compared with PDDs, the use of DDDs as the measurement of hospital antibiotic use overestimated antibiotic use volumes by 32%, while the use of RDD led to a slight underestimation (–9%)*

2. de With et al, Infection 2009

PID >> DID

Package per inhabitants were a better predictor of antimicrobial resistance than DDD per inhabitant.

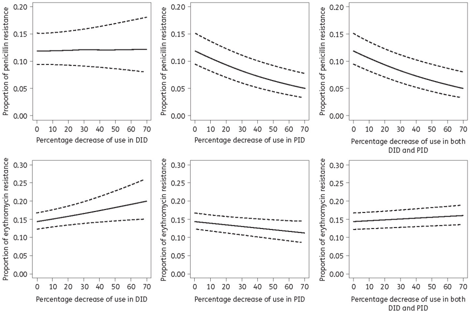


Figure – Average predicted proportion of non-susceptible S. pneumoniae isolates if outpatient antibiotic use had been lower than reported in 2007 (for b-lactam ; top) or 2008 (for TMLS ; bottom) due to a decrease in use in DID (left), PID (middle) or both (right). Bruyndonckx et al, JAC 2015.

Where & when

- Hospital vs. hospital
- Similar or dissimilar wards : ICU, hematology . . .
- At different pace : Yearly, quarterly, monthly : Depending on the amount of data, it is always better to go for the less aggregated data

But if no reliable data to analyze ?

- Typical problem in low income countries
- No reliable data
- Non-prescribed antibiotics
- ...
- $\Rightarrow$ need for alternative methods [3]

3. Padget et al, IJAA 2016

Alternative methods

- *Go and review pharmacy or hospital records or prescription documents*[4]
  - Relatively easy to do
  - Choice of pharmacies or health centre is not random → bias
  - No evaluation of the community level consumption
  - No information on non-prescribed antibiotic sold outside or inside antibiotics
  - No information on patients

4. Chandy SJ et al JAC 2013

Alternative methods

- *The simulated client*[5]
  - An actor presents symptoms and asks for antibiotics
  - Gives proportion of pharmacies providing antibiotics without prescription
  - Focus on the provider, not on the patient
  - No information on antimicrobial consumption at the population level
  - Not adapted for surveillance

5. Bartoloni A, Trop Med Int Health 1998, Llor C, CID 2009

Alternative methods

- *Observed prescribing encounters, patient exit interviews*[6]
  - Can provide DDDs per pharmacy-patients with or without prescription
  - Many variables can be gathered
  - Allows surveillance
  - But selection of pharmacies are not at random → bias
  - No information on total consumption
  - Influence on the provider behaviour, participation fatigue

6. Chandy SJ et al JAC 2013, Esimone et al, Pharm World Sci 2007

Alternative methods

- *Community surveys*[7]
  - Houses are selected randomly and visited by field workers who ask resident about their antibiotic use
  - Allows calculation of unbiased population estimates
  - Accounts for all antibiotic sources, including non-prescribed sources
  - Time consuming and expensive
  - Poorly adapted for surveillance

7. Awad A et al, J Pharm Pharm Sci 2005, Saradamma RD et al, Soc Sci Med 2000

Ability of four study types in responding to antibiotic (ATB) consumption investigation needs in low-income countries (LICs).[a]

	Pharmacy/Hospital document review[b]	Simulated client method	Observed prescribing encounters/ Patient exit interview[b]	Community survey
Antibiotic investigation data				
Type and proportion of ATB use	+++	–	+++	++
DDDs per patient	+++	+	+++	+
ATB consumption for defined population and time period	+	+	+	+++
ATB source including all non-prescription sources	–	–	–	+++
Why ATB given	+++[c]	++	+++	++
Factors associated with ATB use	–	+	++	+++
Non-prescription proportion	–	–	++	+++
Provider knowledge, attitudes and beliefs	–	+++	–	–
Patient knowledge, attitudes and beliefs	–	–	++	+++
Study characteristics				
Adapted to monitoring time trends	+++	+	++	+

DDD, defined daily dose.
[a] +, poor; ++, moderate; +++, good; –, not applicable.
[b] Using non-exhaustive sample of centres/pharmacies.
[c] If including patient records.

Take home message

- Use density (Daily dose per 100 patient-days)
- PDD if possible rather than DDD, or PID
- Start hospital wide, then go for high consumer wards (ICU, hematology etc)

Thank you for your attention

Questions ?