Usage of antimicrobial drugs in food producing animals

In the Netherlands and some other European countries

62nd EAAP Annual Meeting, August 31, 2011

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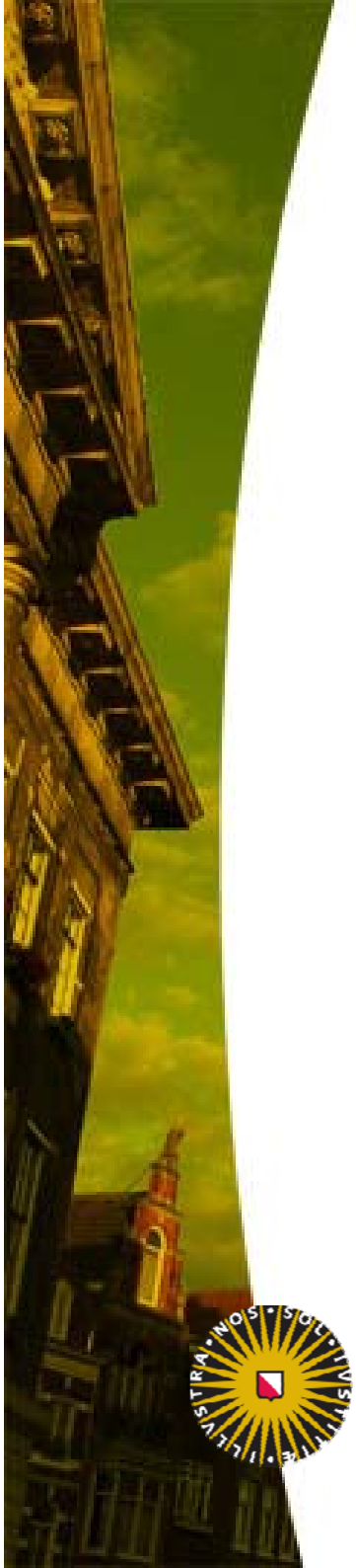
Universiteit Utrecht



Program

Introduction

Ways of quantifying drug use

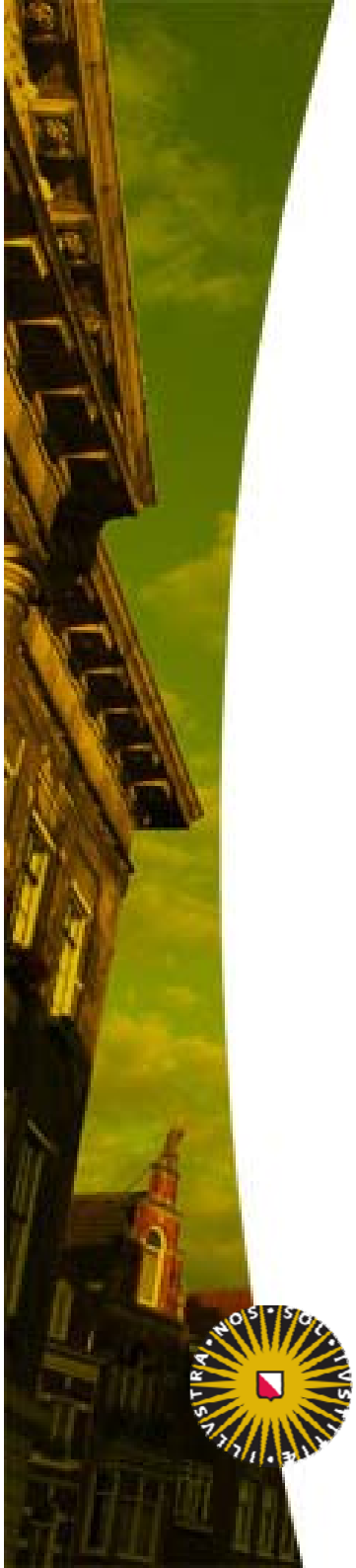
Aims of quantifying antimicrobial drug use

Dutch method I: Maran method

Dutch method II: under construction

Prerogatives for success of an European method

Take home message



CV

Worked in four hospital pharmacies between 1991 and 2007; tasks amongst others therapeutic drug monitoring of anti epileptics and some antimicrobial drugs

In 2007 started at the faculty of Veterinary Medicine of the Utrecht University as head of pharmacy; traditionally source of conversion data for veterinary drugs; start coincided with historical “low” in Dutch antimicrobial usage

Sales of pharmaceuticals in 2010 in the Netherlands

Drugs for human use total: m€ 6.000

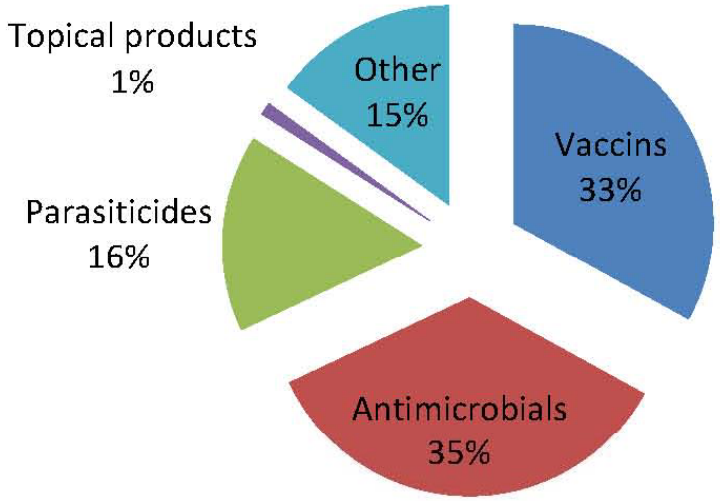
Comprising 6% antibiotics (m€ 360)

Veterinary drugs total: m€ 250

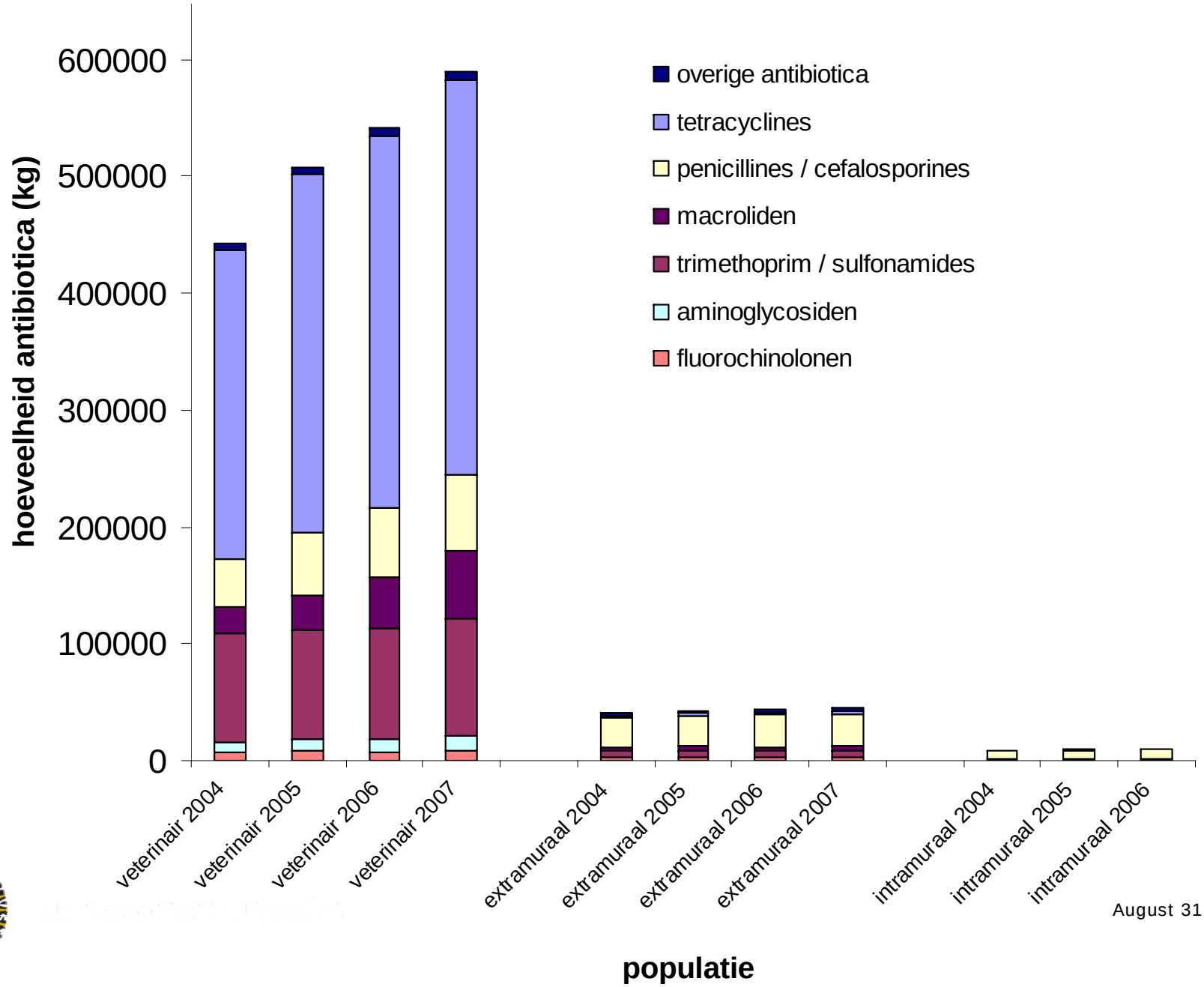
Comprising 35% antibiotics (m€ 87,5)

(>99% for food producing animals)

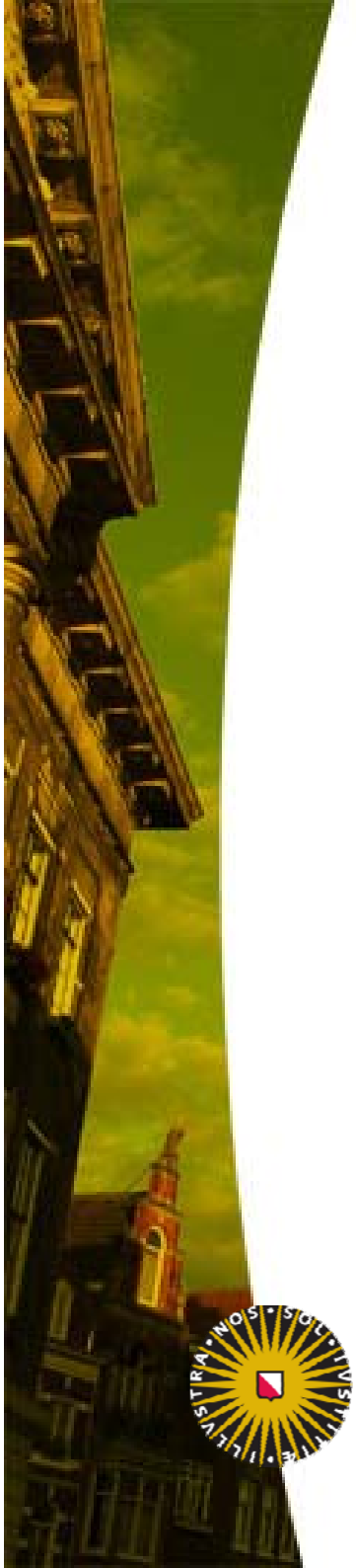
15% non infectious disease related drugs (fertility and companion animals)



Dutch antibiotics consumption in kg



voorpagina Chemisch Weekblad, maart 2009



Human versus veterinary antimicrobial usage monitoring

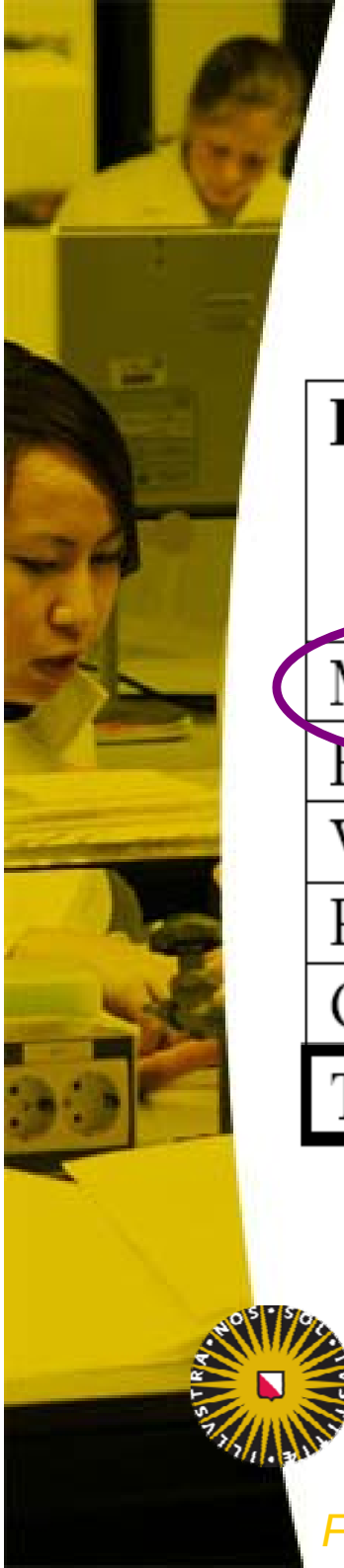
Human (DDD/ATC) monitoring and surveillance

- Related to therapeutic group and therapeutic goal; no interference of substances with different potencies, compare doxycycline (DDD=0,1g) and oxytetracycline (DDD=1g) in one therapeutic group
- Related to population

Veterinary reports

- Aggregated therapeutic groups in kg, aggregation method is often unclear, eg aminoglycosids orally and parenterally in one group
- Relation to population is not standardised: related to meat production or life weight of livestock

Diffuse and ineffective communication on this topic



FIDIN sales data

Diersoorten	Kg actieve stof (x 1000) in 2005	verschil t.o.v. 2004		% van het totale gebruik
		kg (x 1000)	%	
Multi-species	395	48	14 %	78 %
Rund/kalf	21	- 15	-42 %	4 %
Varken	89	24	37 %	18 %
Pluimvee	1	0	0 %	0 %
Gezelschapsdieren	2	-1	- 33 %	0 %
Totaal	**508**	**55**	**12 %**	**100 %**

FIDIN antibioticarapportage 2005, FIDIN werkgroep antibioticabeleid

Pharmaceutical Industry

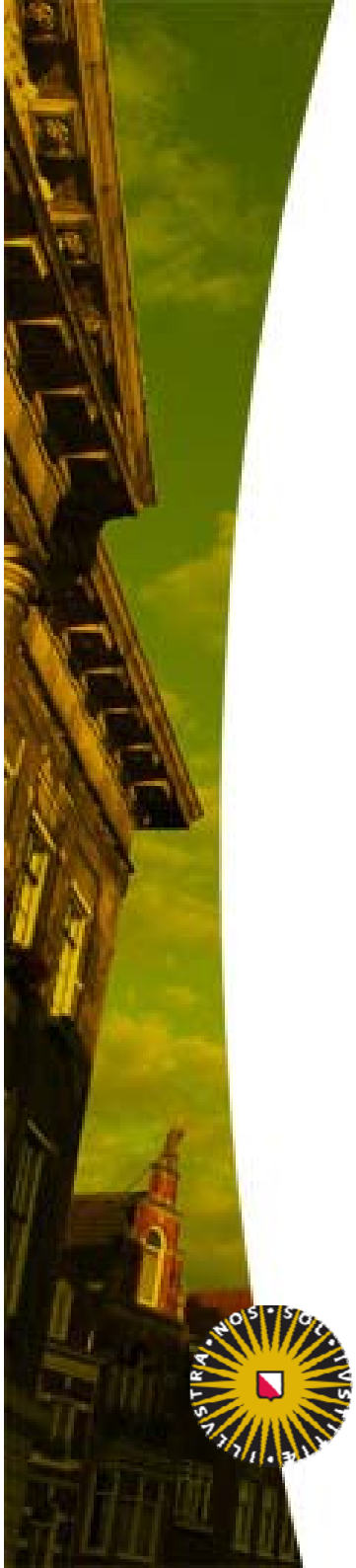
Substitution of oxytetracycline with doxycycline

(based on usage in 2004, assuming factor 2 dosing difference)

	kg
penicillins / cephalosporins	41040
tetracyclines	132010 ~~264020~~
macrolides	22910
aminoglycosides	8580
fluoroquinolones	6880
trimethoprim / sulfonamides	93000
other	6000
total	310220 ~~442430~~

-30%

Bron: Maran 2008



threats

- Empty pipeline of new groups of antimicrobials
- Environmental persistence of newer substances due to higher stability

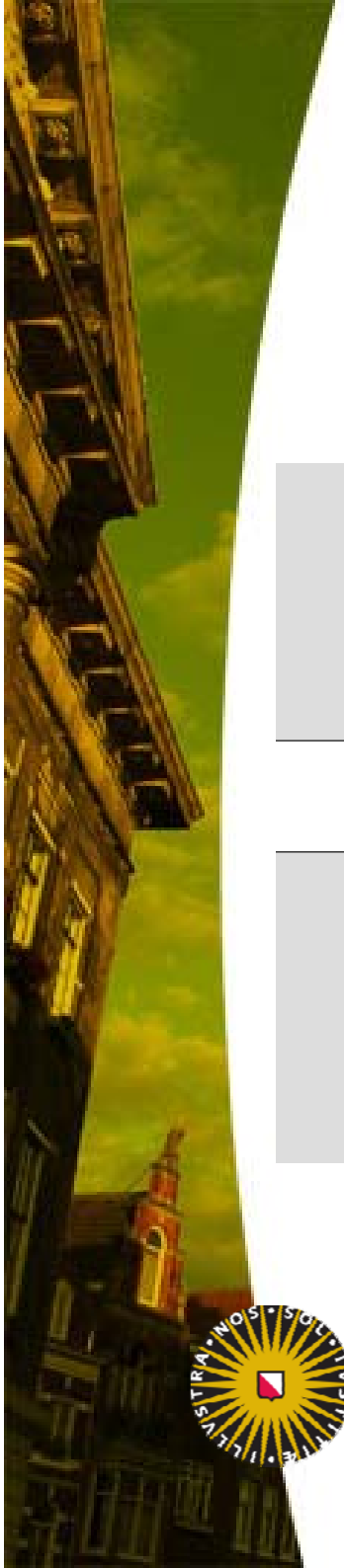
- Emerging multi-resistant pathogens

  (MRSA, Coli and Klebsiella carrying ESBL or KPC, EHEC, VRE, clostridium difficile)
- Zoonoses and penetration (e.g. Q fever, MRSA carrier ship)

Knowledge transfer: sharing knowledge adds value

Ways for interpretation of available data on veterinary antimicrobial consumption

Universiteit Utrecht



Community

Regulatory affairs world wide?

WHO Collaborating Centre
for Drug Statistics Methodology

Norwegian Institute of Public Health, P.O.Box 4404 Nydalen, 0403 Oslo, Norway. Tel: +47 23 40 81 60. Fax. + 47 23 40 81 46
Visiting address: Marcus Thranesgate 6, 0473 Oslo, Norway

ATC/DDD

ATCvet

August 31, 2011

ATC (vet)

Anatomical Therapeutic Chemical grouping of substances

<u>WHO defined ATC-vet</u>

Penicillins = **Q**J01C or QJ51C

Tetracyclins = **Q**J01A

Doxycylin = QJ01AA02

Oxytetracyclin = QJ01AA01

Aminoglycosides = QA07A or QJ01G

Gentamycin orally = QA07AA91

Gentamycin injection = QJ01GB03

Veterinary standardisation of antimicrobial consumption?

WHO defined ATC-vet

Penicillins = **Q**J01C

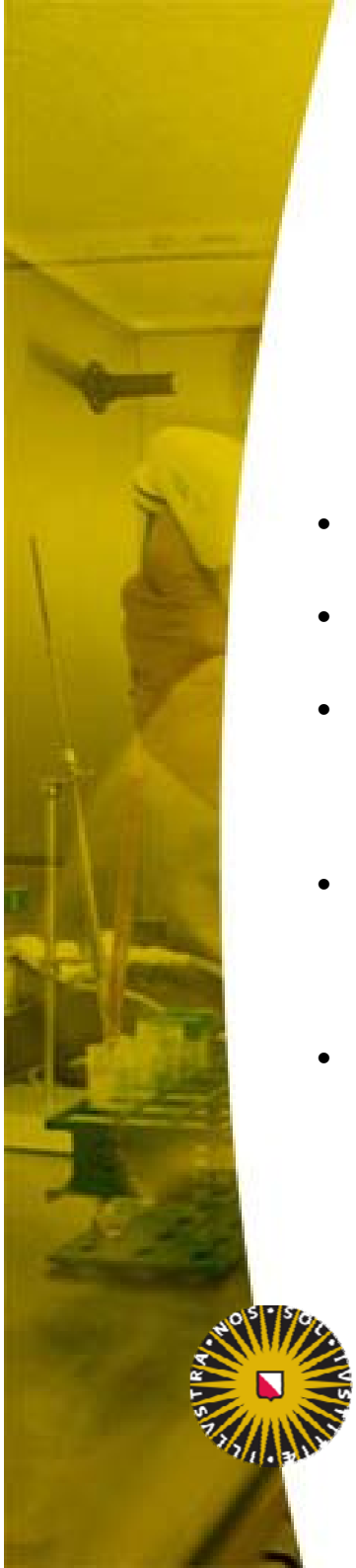
Tetracyclins = **Q**J01A

Dutch approach to veterinary DDD:

1x per day 10 mg***/*kg** = 10 mg***/*kg**

4x per day 10 mg***/*kg** = 40 mg***/*kg**

1x per week 10 mg***/*kg** = 1,43 mg***/*kg**



Available data on Dutch antimicrobial consumption
The Dutch method I

LEI / MARAN

- A **sample** (representative selection) of husbandries
- extracting specified antibiotics from the veterinarian invoices
- applying the nationally defined dagdoseringen for every authorized medicine in The Netherlands, per species and per kg
- converting the declared amount of medicine to treatable animal bodyweight
- relate to the mean present total bodyweight on the husbandry: **compute mean daily doses per animal year**

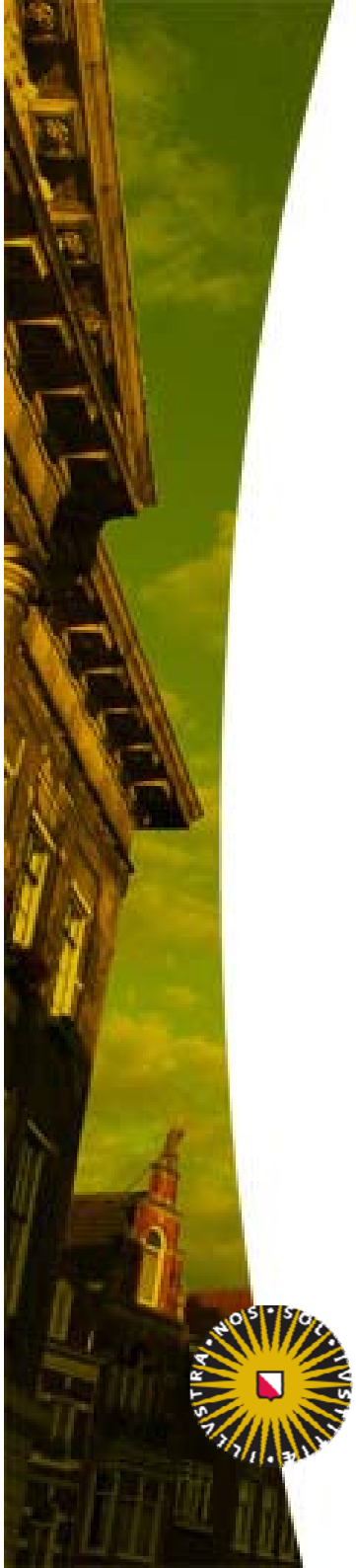
Research

“dagdoseringstabel” Pharmacy faculty Veterinary Medicine

A	C	Q	T	W	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM
.naam	reg_nr	.werkzame_stof	.ATC_vet (werkzame stof)	.opmerkingen	correctiefactor werkingsduur	behandelbare kg pluimvee per verp	pluimveedosering werkzame stof (mg/kg)	dosering rund (g of ml of stuk/kg/dag)	correctiefactor werking	behandelbare kg rundvee per verp	rundvee dosering werkzame stof (mg/kg)	dosering kalf / niet melkgevend rund (g of ml of stuk/kg/d	correctiefactor werkingsduur	behandelbare kg kalf per verp	kalf dosering werkzame stof (mg/kg)	dosering varken (g of ml of stuk per kg/dag)	correctiefactor werkingsduur	behandelbare kg varken per verp
avuloxil 1 injector	9427	amoxicilline/clavulaanzuur	QJ51CR02	3 giften met 12 uur tussenpoos WT m 4 dgn				0,003333		300	0,833333							#DIV/0!
amo-colmix WO, 1 g	8060	amoxicilline/colistine	QJ01RA01	dubbeltherapie: gift/2 = dagdosering				0,1335	2	7,490637	23,496					0,1335	2	7,490637
amoxycolin, 1 ml	9081	amoxicilline/colistine	QJ01RA01	dubbeltherapie met halve dagdoseringen…				0,1		10	11,3	0,1		10	11,3	0,1		10
paracilline oplosbaar poed	4256	amoxicilline	QJ01CA04			40	17,4									0,012		83,33333
albipen LA, 1 ml	7828	ampicilline	QJ01CA01	doseringsinterval 48 uur: 1gift/2 =dagdosering				0,075	2	13,33333	7,5	0,075	2	13,33333	7,5	0,075	2	13,33333
albipen 15%, 1 ml	8206	ampicilline	QJ01CA01					0,05		20	7,5	0,05		20	7,5	0,05		20
curaclox mastitis injector,	8843	ampicilline/cloxacilline	QJ51CR50	3 giften met 12 uur tussenpoos WT m 5 dgn				0,003333		300	0,916667							
prevaclox, 1 injector	8952	ampicilline/cloxacilline	QJ51CR50	wt melk 49 dagen				0,001667		600	0,458333							
orbenin dry cow, 1 injector	1381	cloxacilline	QJ51CF02	wt melk 47 dagen				0,001667		600	0,833333	0,001667		600	0,833333			
rilexine 200 LC, 1 injector	9348	cefalexine	QJ51DA01	4 giften met 12 uur tussenpoos WT m 2 dgn				0,003333		300	0,666667							
cobactan 7,5% LA, 1 ml	10417	cefquinome	QJ01DE90	2,5 mg/kg, doseringsinterval 48 uur 2 giften; gift/2				0,016667		60	1,25	0,016667		60	1,25			
excenel RTU, 1 ml	10061	ceftiofur	QJ01DD90					0,02		50	1					0,06		16,66667
naxcel, 1 ml	10315	ceftiofur	QJ01DD90	>5 dagen werkzaam: gift/5 = dagdosering!							0					0,01	5	100
colistine 1200 topdressing	5901	colistine	QJ01XB01			8	7,89	0,125		8	7,89	0,125		8	7,89	0,125		8
colistine 4800 WSP, 1 g	7733	colistine	QJ01XB01			40	6,312	0,025		40	6,312	0,025		40	6,312	0,0208		48,07692
danocin 180, 1 ml	10212	danofloxacin	QJ01MA92					0,033333		30	6	0,033333		30	6			
dicural orale oplossing, 1m	9694	difloxacine	QJ01MA94			10	10											
dicural injectie 50 mg/ml,	9947	difloxacine	QJ01MA94					0,05		20	2,5							
soludox 50%, 1 g	10275	doxycycline	QJ01AA02			25	18	0,03		33,33333	13,5					0,02		50
baytril 5% injectievloeistof,	2054	enrofloxacin	QJ01MA90					0,075		13,33333	3,75	0,1		10	5	0,075		13,33333
baytril oplossing 2,5% ora	2912	enrofloxacin	QJ01MA90					0,2		5	5	0,2		5	5			
Phenoxypen WSP 325 mg	10333	fenoxymethylpenicilline	QJ01CE02			17,5439	16,701									0,03414		29,29115
nuflor, 1 ml	7993	florfenicol	QJ01BA90	40 mg/kg, 4dgn werkzaam = registratie	2	15	20	0,033333	4	30	10	0,033333	4	30	10	0,066667	2	15
duphacycline 300 extend,	8290	oxytetracycline	QJ01AA06	30 mg/kg 5-6 d werkzaam: gift/5,5=dagdos. 20mg/k			0	0,018182	5,5	55	5,454545	0,018182	5,5	55	5,454545	0,018182	5,5	55
oxykel-10 LA, 1 ml	3548	oxytetracycline	QJ01AA06	geen LA dosering geregistreerd								0,1		10	10,0347	0,1		10
engemycine 5%, 1 ml	4122	oxytetracycline	QJ01AA06	20 mg/kg 3-4 d werkzaam: gift/3,5=dagdos.				0,114286	3,5	8,75	5,314286	0,114286	3,5	8,75	5,314286	0,114286	3,5	8,75
alamycine aerosol, bus a	8284	oxytetracycline	QD06AA03	10 behandelingen per 100 ml (cp)				0,000143		7000	0,664286							
pirsue 1 injector	10153	pirlimycine	QJ51FF90	8 giften met 24 uur tussenpoos WT m 5 dgn				0,001667		600	0,083333							
norocillin 300, 1 ml	2723	benzylpenicilline	QJ01CE01					0,033		30,30303	5,643	0,033		30,30303	5,643	0,033		30,30303
sulfaquinoxaline natrium, 1	1503	sulfaquinoxaline	QJ01EQ16			25	37,2											
nageboorte kapsule TTC-2	8260	tetracycline	QG51AA02					0,001667		599,88	3,080952							
tiamutin 10% injectie, 1 m	8014	tiamulin	QJ01XX92													0,15		6,666667
drinkmix tiamulin 10%, 1 g	7538	tiamulin	QJ01XX92													0,08		12,5
micotil 300, 1 ml	9448	tilmicosine	QJ01FA91	72 uur werkzaam: gift/3 = dagdosering!								0,0111	3	90,09009	3,33			
tilmovet, 1 ml	10560	tilmicosine	QJ01FA91			14,2857	17,5					0,1		10	25	0,07		14,28571
trim/sul 80/420, 1 g	2213	trimethoprim/sulfadiazine	QJ01EW10	varken: bigdosering (half 28 dgn!)		10,5263	44,27	0,05		20	23,3	0,05		20	23,3	0,025		40
trimethosulfmix 50%, 1 g	7939	trimethoprim/sulfadiazine	QJ01EW10			11,4025	40,8682	0,05		20	23,3	0,05		20	23,3	0,0375		26,66667

Blad2 Blad1

NUM



Characteristics of the MARAN method

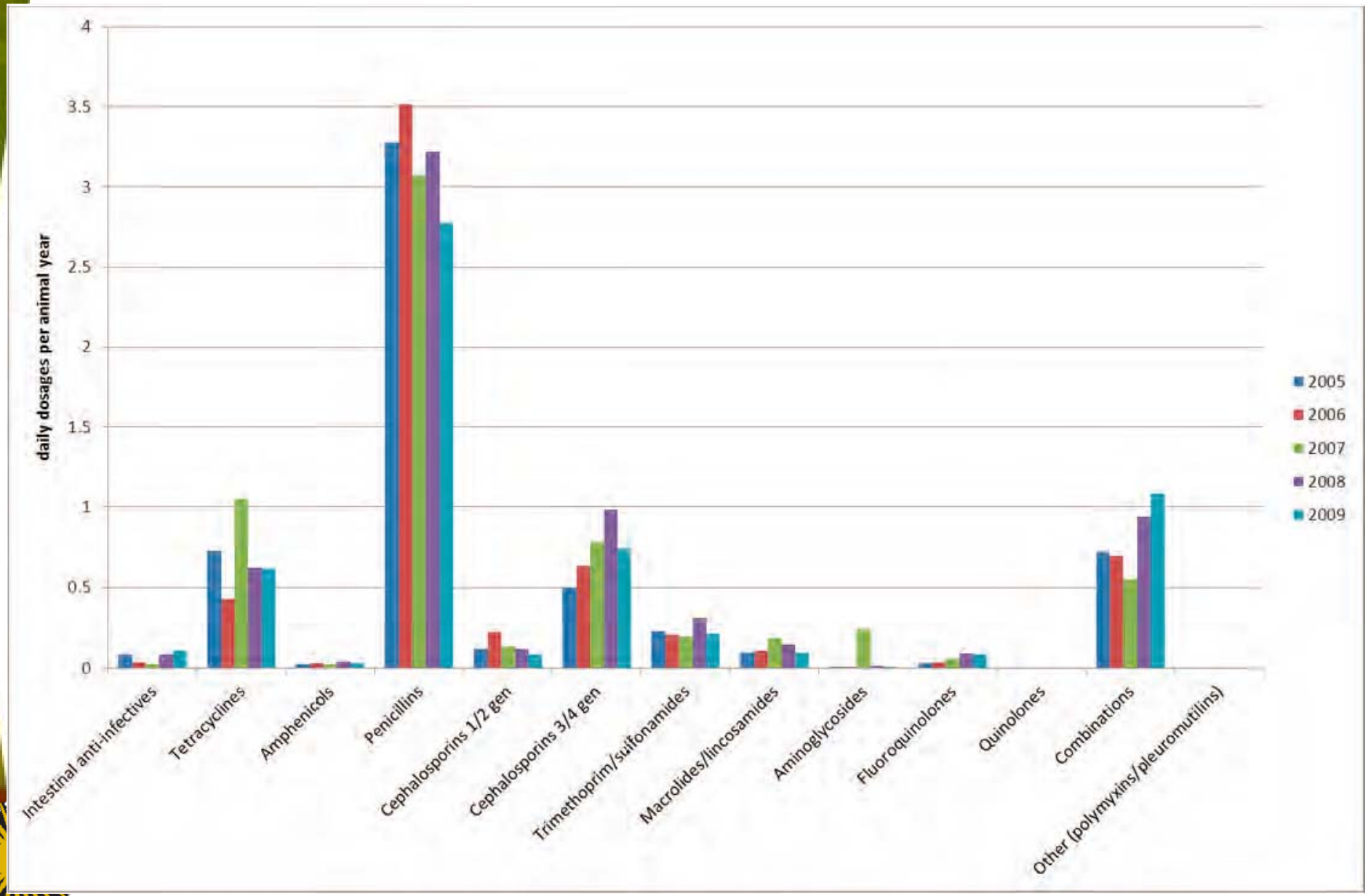
- Acknowledges legal obligation in NL to apply the authorized dosages of veterinary medicines: treatable weight calculated for every single specified medicine

- Population data (number of animals and weights) available

- Still need to make choices for the exposed subgroup of animals: in diary cattle the calves are neglected, in breeding sows the mean weight of 10 piglets and 1 sow is applied

Community

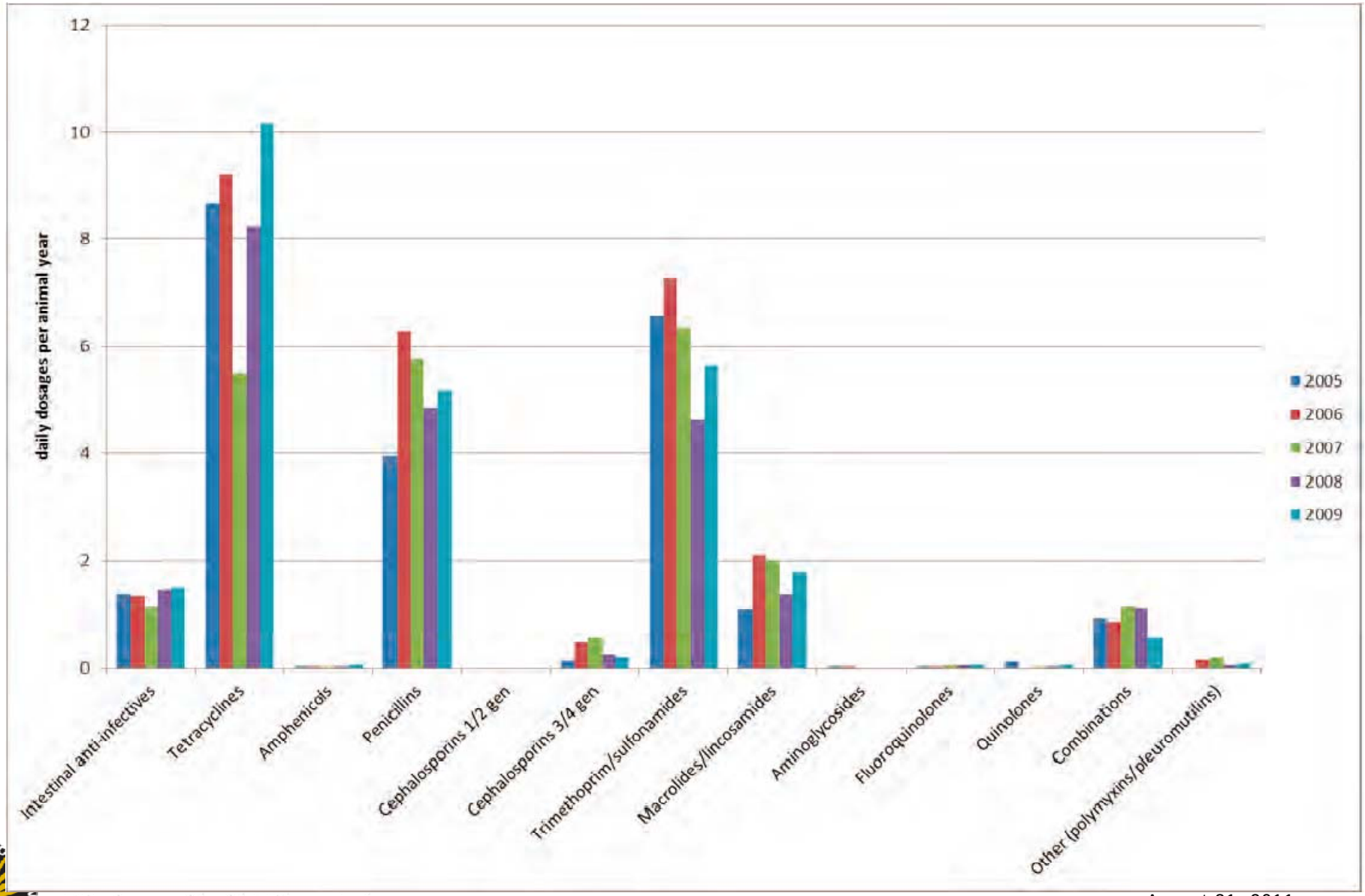
Daily dosages per animal year in dairy cattle



Maran 2009

Community

Daily dosages per animal year in sows / piglets



Maran 2009

Available data on European antimicrobial consumption

Danmap (prescription vet + hum)

Svarm (prescription (since 2003) vet + hum)

Norm-Normvet (sales vet + hum)

Finres (sales vet)

VMD-sales UK (sales vet)

AFSSA-ANMV France (sales vet)

Swissmedic, Swiss Agency for Therapeutic Products (sales vet)

Germap (sales vet)

BelVet-Sac (sales vet)

FIDIN (sales vet)

in kg active substance (accumulated)

Available data on European antimicrobial consumption Denmark

the consumption is measured both in kg active substance and as a National Animal Defined Daily Dose, the latter either as the dose for one kg animal bodyweight (ADDkg) or as the dose for a defined animal body weight x (ADDx), depending on species and age group.

Reasons for more specified analysis

Considering

- Potency differences between active substances
- Dosing differences between species
- ???

Aim

- Linking usage data with resistance data
- Interpretation of shifts in therapy choices
- Anticipating future developments

Reasons for more specified analysis and comparison between countries

- Awareness stimulation!
- Adaptation of formularies

Identifying influence of

- Husbandry system and management
- Strategic choices
- National policies

Knowing

- Populations at risk

Available data on European antimicrobial consumption
The Dutch method II (under construction)

Calculated weighed mean dose per FT group per country

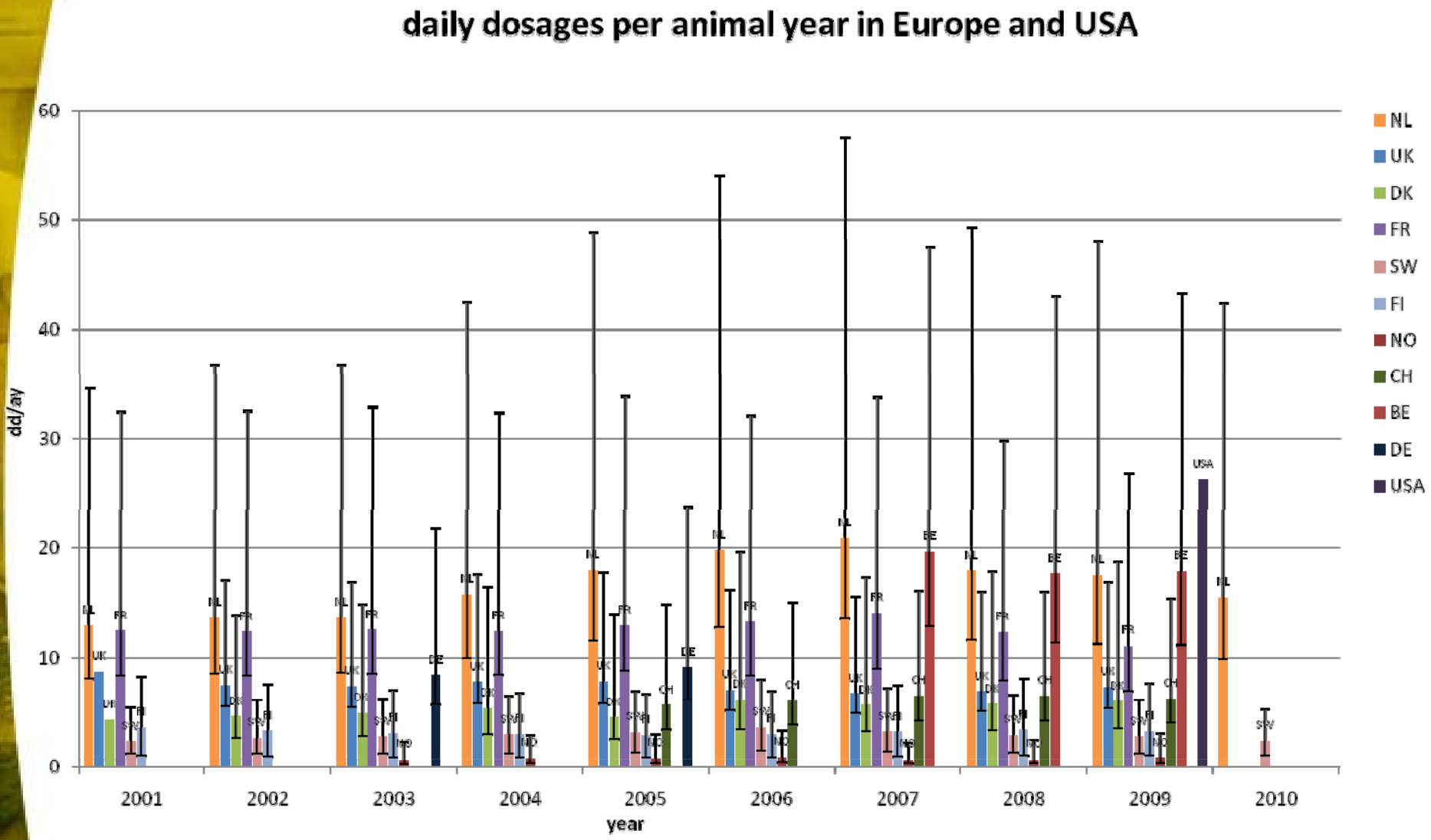
- of all substances in a pharmacotherapeutic group based on Dutch authorized medicines (anno 2011)
- of most important route of administration (mostly oral)
- weighed by livestock composition (kg BW of poultry*dose + kg BW veal*dose + kg BW cattle*dose + kg BW pig*dose)/total kg BW

Interpretation of available kg data possible, at least some consideration of

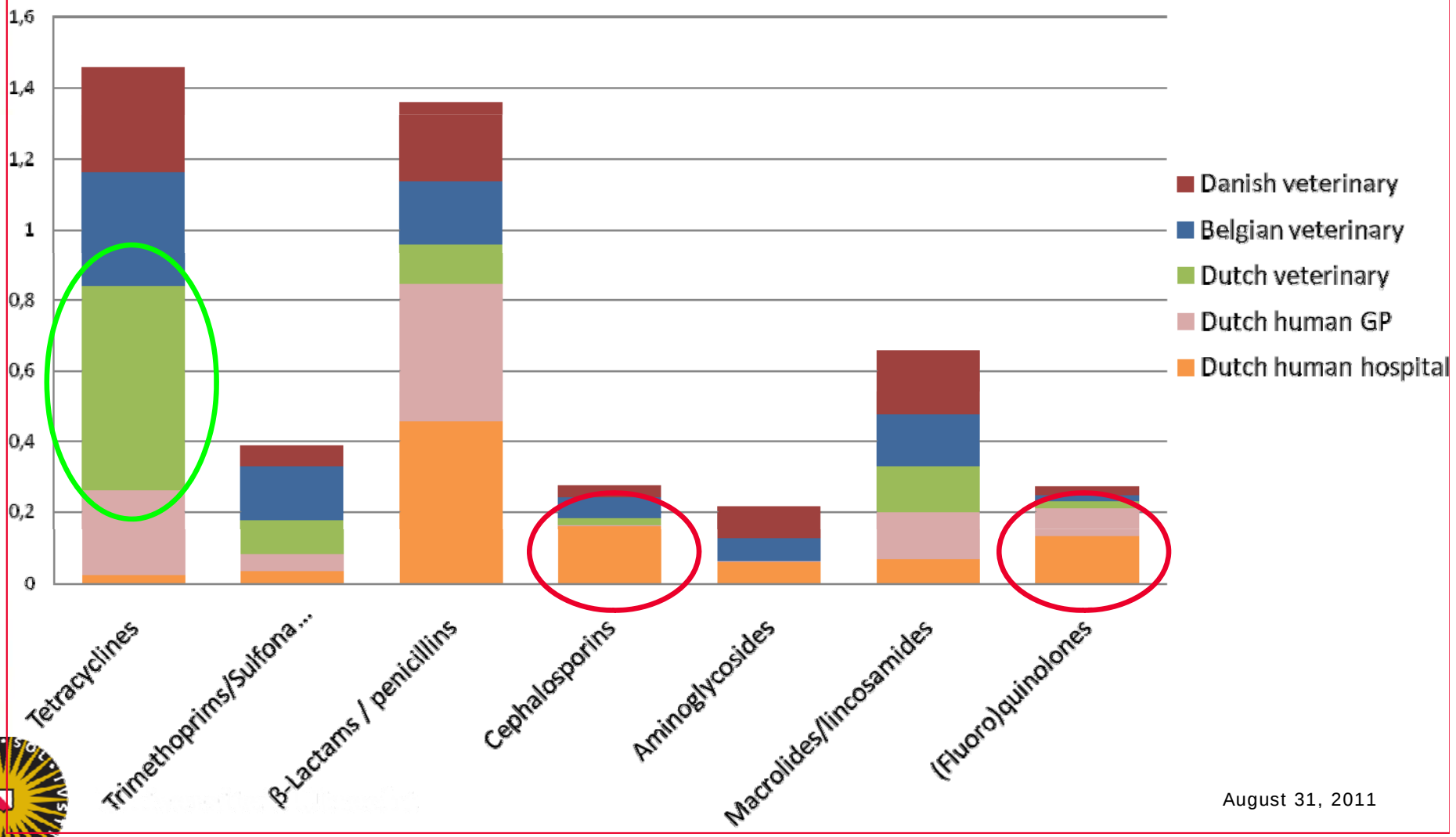
- differences in potency between pharmacotherapeutic groups
- differences in national dosing related to livestock composition

Available data on European antimicrobial consumption
The Dutch method II, calculated national doses

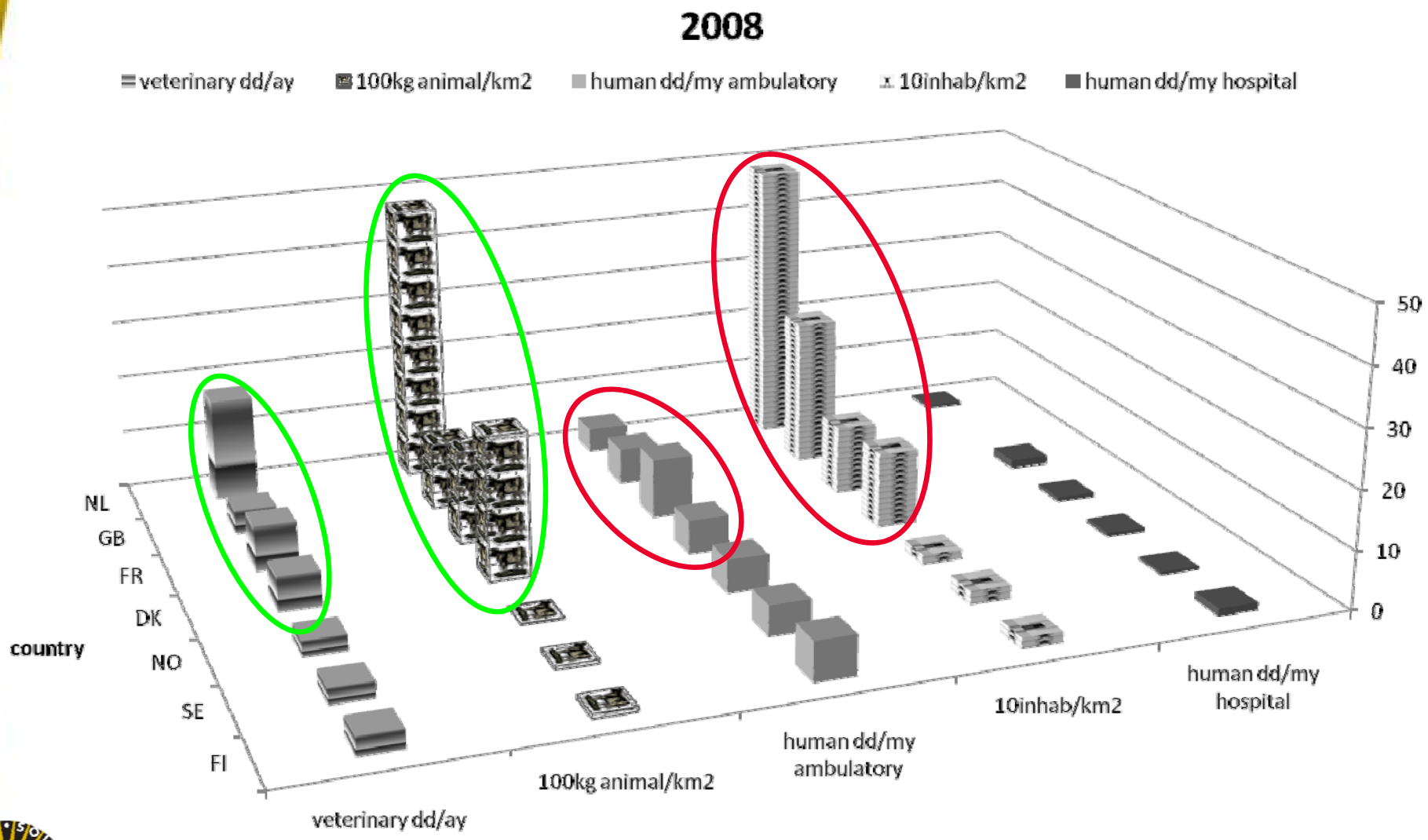
Pharmacotherapeutic group	ATC vet	mg/kg min (often UK)	mg/kg Max (often FI)
Tetracyclines	QJ01AA_QD06AA_QG51AA	6,69	13,65
Oral antiinfectives / ionophores	QA07AA	8,04	10,20
Amphenicols	QJ01BA	10,37	12,66
Trimethoprims/Sulfonamides	QJ01EA / EQ / EW	20,84	28,52
β-Lactams / penicillins	QJ01C_QJ51C	12,94	18,21
Cephalosporins 1/2	QJ01DB / DC_QJ51RD_QJ51DA3_QG51AX	0,67	0,67
Cephalosporins 3/4	QJ01DD / DE_QJ51DA9	1,14	1,83
Aminoglycosides	QJ01G	6,94	9,25
Macrolides/lincosamides	QJ01FA / FF_QJ51FF	4,77	17,93
Quinolones	QJ01MB	17,69	21,08
Fluoroquinolones	QJ01MA	3,03	5,05
Combinations	QJ01R_QJ51R	1,11	22,76
Other (polymyxines, pleuromutilins)	QJ01AA_QD06AA_QG51AA	9,98	20,13


daily dosages per animal year in Europe and USA
dd/ay
60
50
40
30
20
10
0
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
year
NL
UK
DK
FR
SW
FI
NO
CH
BE
DE
USA

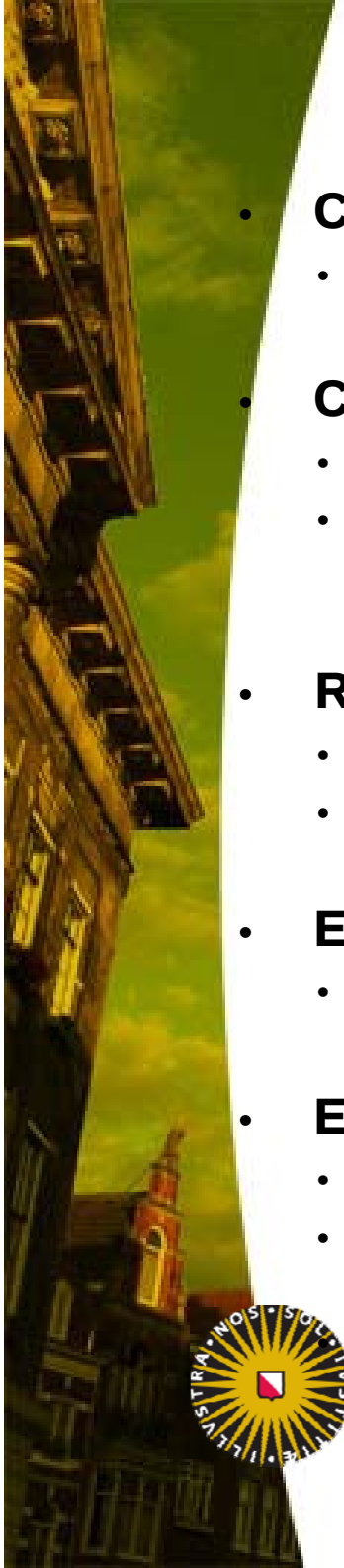
fraction of total use (in DDD) for main therapeutic groups Dutch human vs Dutch, Belgian and Danish veterinary (2009)



Relationship antimicrobial use - population density



antimicrobial drug consumption / amount of animals or humans per square km



Community

European method

- **Consequent application of correct ATC vet**
  - Local identification of medicine: veterinarian or husbandry
- **Collection of consumption data connected to species**
  - Local calculation of treatable kg
  - Local conversion to ADD (even subgroup analysis?) for individual husbandry management purposes
- **Report to national database**
  - ATCvet + ADD for monitoring purposes
  - ATCvet + treatable kg + species for national calculation of ADD
- **European collection of data**
  - Per country per species: ATCvet + treatable kg
- **Evaluation of data**
  - Identifying risk factors for societal biological safety
  - Imposing international guidelines to prevent malpractices or black market for antimicrobials
  - Creating awareness in professionals AND civilians on societal stewardship

Community

European method prerogatives

- **Consequent application of correct ATC vet**
  - Part of SPC (Summary of Product Characteristics)
- **Collection of consumption data connected to species**
  - ADD consensus in member states of Europe, idem in SPC
- **Report to national database**
  - National source database available for all veterinary drugs
  - Safe environment for husbandries / veterinarians to report usage or prescription data
  - Involvement of all parties (veterinarians, husbandry cooperations, industry)
- **European collection of data**
  - Per country (preferably per species): ATCvet + treatable kg
  - Nominator data consensus (life weight livestock)
- **Evaluation of data**
  - Independent professionals
  - Undisclosed publication

Issues to consider!

- **Antimicrobial drugs, related to those essential for human use:**
  - 3rd and 4th generation cephalosporins (ceftiofur, cefquinome, cefoperazone, cefovecin)
  - modern (2nd generation?) fluoroquinolones (enrofloxacine, marbofloxacine, danofloxacine)
  - colistin (?)

- **Antibiotics with long $T_{1/2}$ or extended release formulation**
  - tulathromycine (Draxxin®)
  - gamithromycine (Zactran®)
  - tilmicosin (Micotil®)
  - florfenicol (Nuflor®)
  - oxytetracycline (several LA products)
  - ampicilin (several LA products)
  - (tildipiron (Zuprevo®))

- **Essential antibiotics with extended release formulation or intrinsic long half-life**
  - ceftiofur (Naxcel®)
  - cefquinome (Cobactan® LA)
  - cefovecin (Convenia®)

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contributed to data collection and interpretation

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