06 - Establishing DDDvet and DCDvet – history and state of play

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ESVAC Stakeholders meeting, 2 March, 2016, EMA, London

Veterinærinstituttet
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Outline

- History
- Aim of
  - Establishing DDDvet and DCDvet
  - Principles
- Exceptions from principles
- Publishing of the lists of DDDvet and DCDvet

History

- WHO consultation in Oslo, Norway, 10 - 13 September 2001: Concluded that a concept like the DDD (defined daily dose) used in human medicine should be developed for the use in veterinary medicine
- Also recommended by Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific assessment in Geneva, 1 – 5 December 2003.
- During a WHO Consultation in 2001, an informal group of experts discussed suggested the work to be started by the WHO Collaborating Centre for Drug Statistics Methodology in collaboration with the ATCvet Working Group.
- November 2001: The ATCvet Working Group decided to develop a parallel to the DDD for the use in veterinary medicine.

History cont.

- **November 2003:** The ATCvet Working Group of the WHO Collaborating Centre for Drug Statistics Methodology (WHO CC) agreed on
  - Draft guidelines for assignment of Defined Daily Doses for veterinary medicines (DDD_{animal}) and
  - Preliminary $DDD_{animals}$ for selected groups of antibacterials used in selected food producing animals
- **January 2004:** WHO CC published these documents on their website and e-mailed these to interested persons and organisations for comments.

History cont.

Addressed during annual meeting ATCvet WG November 2004

- Summary comments received:
  - a thorough discussion on how to express drug usage data in veterinary medicine for the various purposes, e.g., link with antimicrobial drug resistance data, was requested.
  - it was highly recommended to involve relevant experts, representatives of relevant international organizations as well as from various countries in the decision making process in order to cover the diversity of veterinary prescribing practices and to ensure transparency.
- The ATCvet WG supported these opinions and concluded that further international discussions were necessary.
  - It was decided not to terminate, but to postpone the assignment of DDD_{animal}.

Conclusion: It was too early as there still was confusion with respect to what purposes such a unit should and could serve; relevant stakeholders should be included in the process.
Note that in 2004 only one paper and two national surveillance reports had been published using DDD animals (next slide).

History cont.

1999: Norwegian - Swedish study applied DDD diary cow as unit of measurement

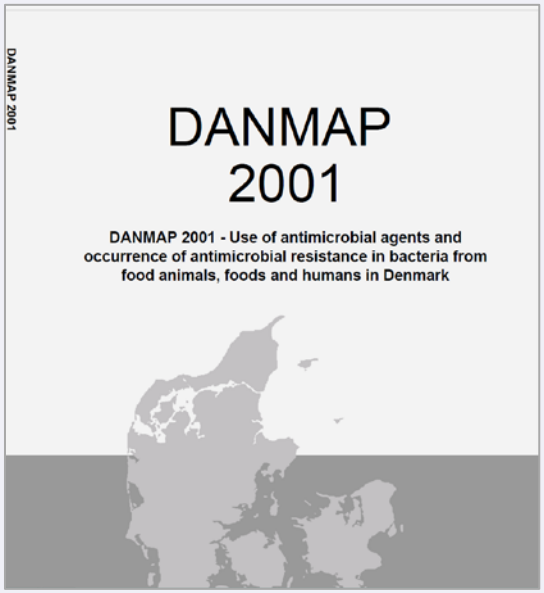
Prev Vet Med. 1999 Sep 30;42(1):45-55.

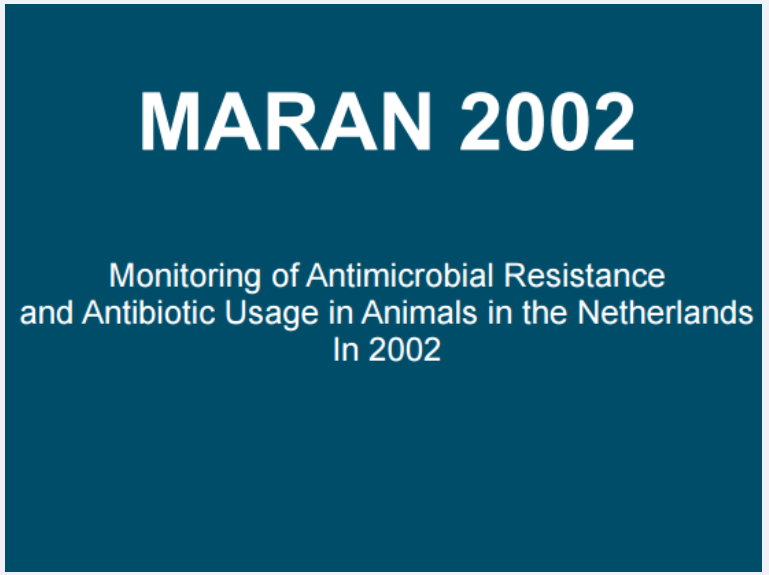
The usage of veterinary antibacterial drugs for mastitis in cattle in Norway and Sweden during 1990-1997

Grave K[1], Greko C, Nilsson L, Odensvik K, Mørk T, Rønning M. ← WHO CC as co-author

2001: Denmark applied ADD for reporting of VetStat data – i.e. consumption data by species consumption data - for the first time

2002: Netherland applied DDD for reporting of data on consumption in pigs and poultry for the first time





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History cont.

- What happened between 2004 and 2013?
  - One more EU countries had established national technical units of measurement

2009: France applied a unit similar to DCD to report 2008 data by species (based on DDD)

  - Numerous papers on DDD animals published

- Meaning that
  - Experience gained by more countries/experts
  - Purposes of DDD_{animal} had been subjected to discussion

2013 appropriate TIMING

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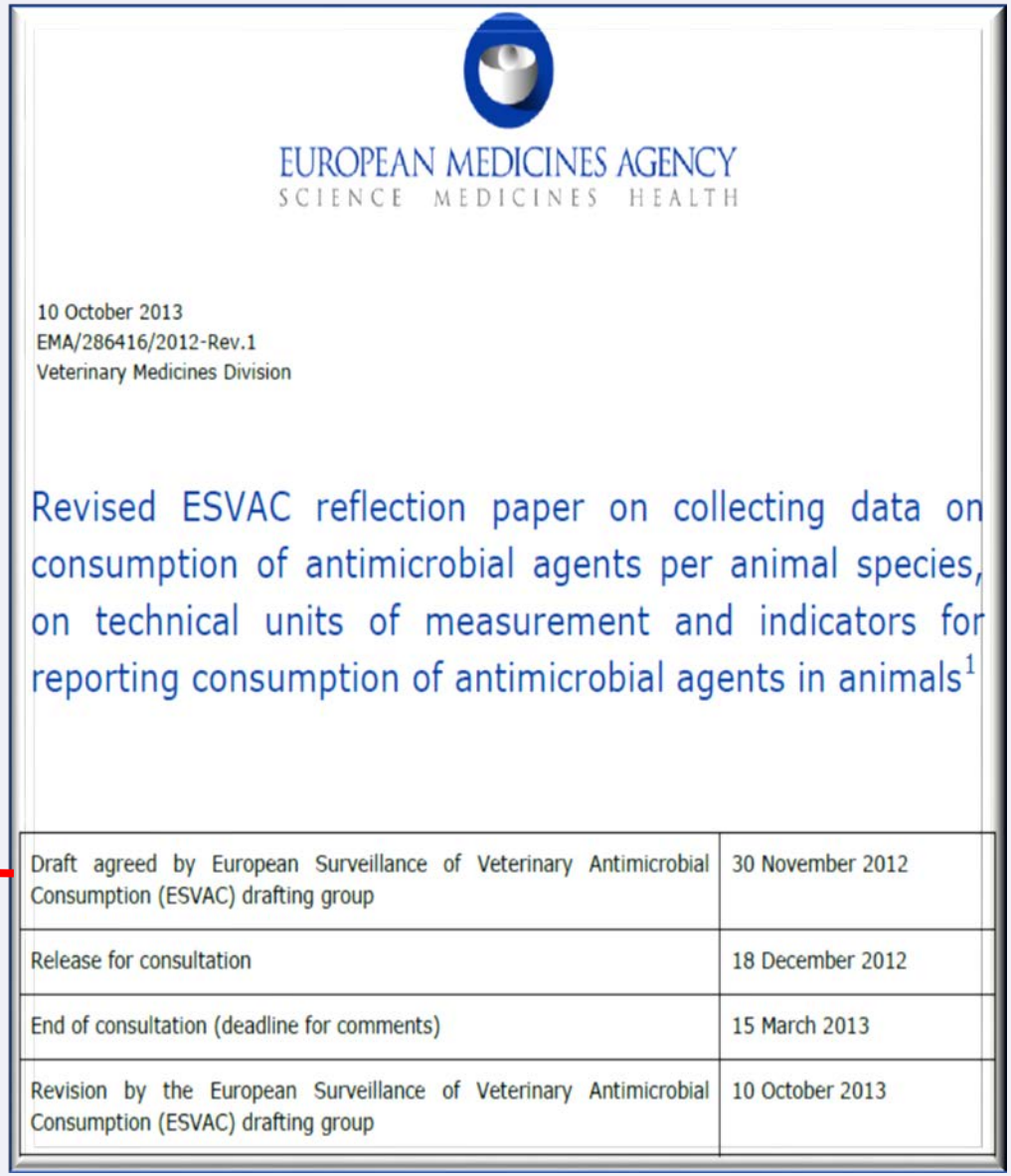
History cont.

Since only national DDD animals available - need for harmonisation across EU/EEA area.

Reflection paper suggests to develop guidelines on how to assign DDDA and DCDA values for pigs, poultry and cattle across EU



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

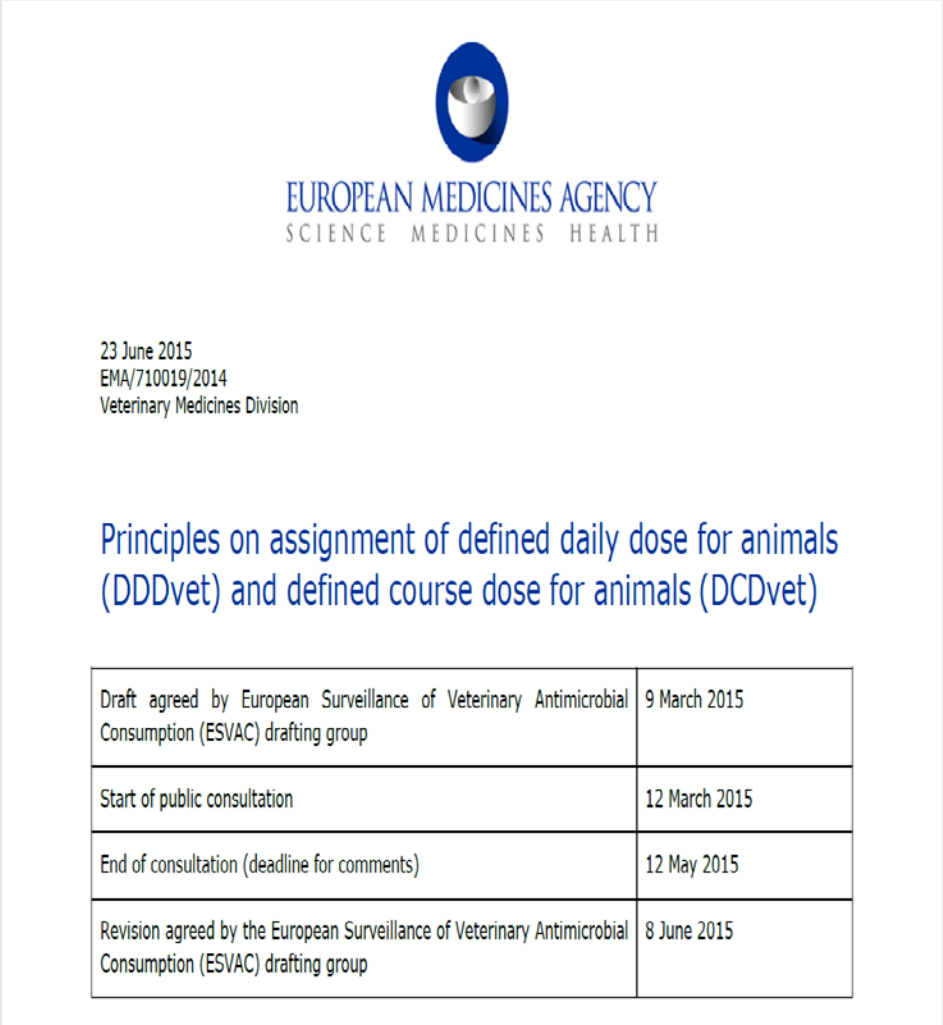
10 October 2013
EMA/286416/2012-Rev.1
Veterinary Medicines Division

Revised ESVAC reflection paper on collecting data on consumption of antimicrobial agents per animal species, on technical units of measurement and indicators for reporting consumption of antimicrobial agents in animals[1]

Draft agreed by European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) drafting group	30 November 2012
Release for consultation	18 December 2012
End of consultation (deadline for comments)	15 March 2013
Revision by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) drafting group	10 October 2013

Methodology published by EMA[1]

ESVAC *ad hoc* working group: Inge van Geijlswijk, Christina Greko, Erik Jacobsen, Irene Litleskare, Gérard Moulin (chair) and Cedric Müntener (until July 2015, see slide 18)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2015
EMA/710019/2014
Veterinary Medicines Division

Principles on assignment of defined daily dose for animals (DDDvet) and defined course dose for animals (DCDvet)

Draft agreed by European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) drafting group	9 March 2015
Start of public consultation	12 March 2015
End of consultation (deadline for comments)	12 May 2015
Revision agreed by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) drafting group	8 June 2015

[1]http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500188890.pdf

Aim of assignment of DDDvet and DCDvet in the context of AMR

- 1. To aid interpretation of patterns and t[illegible]regarding antibacterial resistance;
- 2. As a basis for risk profiling and [illegible]sessment regarding antibacterial drug resistance;
- 3. As a basis for setting ris[illegible]gement priorities;
- 4. As a basis for evalu[illegible] the effectiveness of control measures being imp[illegible]ted;
- 5. To identify e[illegible]g use of antibacterial drugs, e.g. of specific drug[illegible]s such as critically important antibiotics;
- 6. To aid [illegible]arison of usage of antibacterial drugs between and w[illegible]ountries and between time periods etc.;
- 7. [illegible]ess the spread and effect of antibacterial drug [illegible]tion of the environment;
- 8. As a basis for focused and targeted research and development.

Human medicine: follow therapeutic trends main aim

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Aim of the principles

- Serve as a «manual» for EMA/ESVAC for the assignment of DDDvet and DCDvet for antimicrobials
- To ensure
  - Consistency
  - Transparency

Disclaimer: It should be noted that DDDvet and DCDvet are technical units of measurement solely intended for the purpose of drug consumption studies. They should not necessarily be assumed to reflect the daily doses recommended or prescribed. The assigned DDDvet and DCDvet values will nearly always be a compromise. Established DDDvet or DCDvet are not applicable for commercial use such as pricing and analyses of drug costs.

ESVAC Advisory Expert group on DDDvet and DCDvet

- Nominated July 2015
- Terms of reference

  The ESVAC units Expert Advisory Group will specifically provide advice to the ESVAC team:

  • on assignment of DDDvet and DCDvet values;

  • on revision of the principles on assignment of DDDvet and DCDvet as required;

  • in order to improve the DDDvet and DCDvet system;

  • on development of appropriate indicators for reporting species data;

  • on other activities as required.
- Members

  Inge van Geijlswijk, Kari Grave (chair), Christina Greko, Irene Litleskare, Gérard Moulin and Cedric Müntener

Assignment of DDDvet and DCDvet

- Data material
  - Data on dosing obtained from Summaries of Product Characteristics (SPCs) for antimicrobial veterinary medicinal products for broilers, cattle and pigs from nine EU-countries: Czech Republic, Denmark, Finland, France, Germany, the Netherlands, Spain, Sweden and United Kingdom.
  - Assessment of coverage of the data set identified that of antimicrobials sold in 26 MSs in 2012 only two major substances were missing - thiamphenicol and paromomycin. Fore these substances SPC data were collected from the countries that hold the marketing authorization for these
- Methodology
  - Principles

Principles

- *"The assignment of DDDvet and DCDvet will usually be based on the average (arithmetic mean) of all observations of veterinary medicinal products for each species, substance and administration route/form in question given by the SPCs".*
- *"Generally, in cases where the SPC information on dosing is insufficient, e.g. when duration of effect is not clear, information obtained from scientific publications and/or text books will be consulted".*

Pending: Exception from the principles

- For three centrally authorised LA injectable macrolides - gamithromycin, tulathromycin and tildipirosin – the duration of activity were not given in the SPC (long acting due to long biological half-life).
- Search in literature and textbooks provided limited information.
  - Currently, it is explored whether calculating duration of activity by use of pharmacokinetic parameters could be used as a method to obtain a valid surrogate for the duration of activity.
  - Using this approach (gamithromycin, tulathromycin and tildipirosin) - an exception from the principles (see previous slide).

Tentative timelines

- Lists of DDDvet and DCDvet lists to be published in April
  - Sent embargoed to MSs 2 weeks before
  - Sent embargoed to stakeholders 1 week before
- DDDvet and DCDvet for gamithromycin, tildipirosin and tulathromycin injectables will be amended to the lists once assigned
  - Document on the methodology will be published at same time
- Next step: maintenance of the DDDvet and DCDvet system