WHO Collaborating Centre for
Drug Statistics Methodology

Norwegian Institute of Public Health

WHO ATC/DDD methodology: Classifying and quantifying drug use

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Outline

- The ATC/DDD methodology
  - definitions, purpose, structure and principles
- The WHO Collaborating Centre and the Working Group
- Procedures for establishing ATC codes
- Applications of ATC/DDD

Definitions

- ATC
  Anatomical Therapeutic Chemical classification

- DDD (Defined Daily Dose)
  The assumed average maintenance dose per day for a drug used for its main indication in adults

History

- Developed in Norway (in collaboration with European researchers) in the early seventies
- 1976, the “Nordic Council on Medicines” decided to publish “Nordic Statistics on Medicines” using the methodology
- 1982, The WHO Regional Office for Europe established the WHO Collaborating Centre for Drug Statistics Methodology
- 1996, agreement with the World Health Organisation in Geneva concerning the global activity of the Centre

Main purpose

"International language for drug utilization monitoring and research"

- to serve as a tool for presenting drug utilization monitoring and research in order to improve quality of drug use
- to group drugs to facilitate retrieval

The WHO Collaborating Centre for Drug Statistics Methodology

- Located in the Department of Pharmacoepidemiology at the Norwegian Institute of Public Health

Terms of reference

- ATC coding
- Establish defined daily doses (DDDs)
- Review and revise as necessary ATC/DDD
- Stimulate use of the system
- Conduct training courses
- Technical support and capacity building

WHO International Working Group for Drug Statistics Methodology

- Nominated in December 1996
- Equal representation from the different regions in the world
- 12 members from:
  Australia, Croatia, Cuba, Denmark, India, Japan, Morocco, Pakistan, USA, and Zimbabwe
- Observers from: IFPMA and UMC
- Approves all new ATC codes, DDDs and alterations

IFPMA: International Federation of Pharmaceutical Manufacturers Association

UMC: The Uppsala Monitoring Centre (WHO Collaborating Centre for International Drug Monitoring)

ATC classification

Anatomical

Therapeutic

Chemical

Inclusion criteria

- New chemical entities or biologicals proposed for licensing in a range of countries
- Well defined chemical entities used in a variety of countries
- Herbal medicinal products assessed and approved by regulatory authorities based on dossiers including efficacy, safety, and quality data

ATC – main groups

- A Alimentary tract and metabolism
- B Blood and blood forming organs
- C Cardiovascular system
- D Dermatologicals
- G Genito urinary system and sex hormones
- H Systemic hormonal preparations, excl. sex hormones and insulins
- J Antiinfectives for systemic use
- L Antineoplastic and immunomodulating agents
- M Musculo-skeletal system
- N Nervous system
- P Antiparasitic products, insecticides and repellents
- R Respiratory system
- S Sensory organs
- V Various

Structure of the ATC code

A	ALIMENTARY TRACT AND METABOLISM (1st level, anatomical main group)
A**10**	DRUGS USED IN DIABETES (2nd level, therapeutic subgroup)
A10**B**	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS (3rd level, pharmacological subgroup)
A10B**A**	BIGUANIDES (4th level, chemical subgroup)
A10BA**02**	METFORMIN (5th level, chemical substance)

Structure of the ATC system

C	Cardiovascular system (1st level, anatomical main group)
C08	Calcium channel blockers (2nd level, pharmacological subgroup)
C08D	Selective calcium channel blockers with direct cardiac effects (3rd level, pharmacological subgroup)
C08DA	Phenylalkylamine derivatives (4th level, chemical subgroup)
C08DA01	verapamil (5th level, chemical substance)

“X groups”

- New 4th levels:
  - only established when at least two substances with marketing authorisations fit in the group
  - a new 4th level should be regarded a benefit for drug utilisation monitoring and research

- X groups: substances not clearly belonging to any existing ATC 4th level

  A10B**X** Other blood glucose lowering drugs excl. Insulins

General principles for ATC classification

- Drugs are classified according to their main therapeutic use
- Normally only one ATC code for each dosage form of a medicinal product
- Several ATC codes:

  Clearly different therapeutic uses according to

  - routes of administration (e.g. topical, systemic)

  - strengths

“Simple” codes

- Linagliptin (e.g. Trajenta): Antidiabetic → DPP-4 inhibitor → A10BH05
- Lamivudine (e.g. Epivir): HIV → Antiviral → J05AF05
- Naratriptan (e.g. Naramig): Antimigraine → $5HT_1$ agonist → N02CC02
- Formoterol (e.g. Oxis): Antiasthmatic → β_2 agonist → R03AC13

Different indications - one ATC code

Example duloxetine (strengths 20, 30, 40 and 60 mg)

- Major depressive disorder
- Diabetic neuropathic pain
- Stress urinary incontinence

Overlapping dosages used for the various indications

ATC code as *antidepressant* (*N06AX21)*

Mapping indication to ATC – often difficult

Bone diseases/osteoporosis	ATC group
Vitamin D and analogues	A11CC
Calcium supplement	A12A
Estrogens/Tibolon/SERM	G03C/G03F/G03X
Parathyroid hormones	H05AA
Calcitonin	H05BA
Bisphosphonates	M05BA/M05BB

Antibiotics in the ATC system main groups

A Alimentary tract and metabolism

D Dermatologicals

G Genito urinary system and sex hormones

J Antiinfectives for systemic use

- **J01 Antibacterials**
- J02 Antimycotics
- J04 Antimycobacterials
- J05 Antivirals

(L Antineoplastic and immunomodulating agents)

P Antiparasitic products, insecticides and repellents

R Respiratory system

S Sensory organs

Several ATC codes – different pharmaceutical forms and therapeutic use

Prednisolone

- A07EA01 (Enemas and rectal foams)
- C05AA04 (Rectal suppositories)
- D07AA03 (Creams, ointments and lotions)
- H02AB06 (Tablets, injections)
- R01AD02 (Nasal sprays/drops)
- S01BA04 (Eye drops)
- S02BA03 (Ear drops)

ATC for combinations

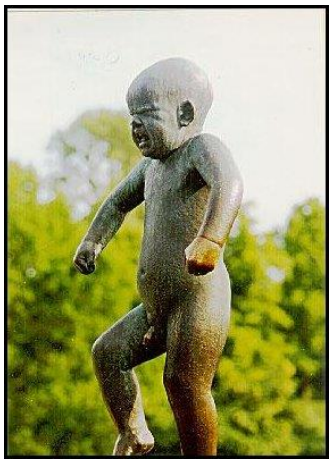
Main principles:

- Combinations are included in separate ATC 5th levels in the same ATC 4th level where the key component is classified
  - Combinations of drugs from different ATC groups
  - Combinations of drugs classified in the same ATC group
- Separate ATC 3rd or 4th levels have been established for “important” combinations

ATC alterations

Alterations of ATC codes may occur in order to reflect changes in drug therapy.

It is important to describe the version of the ATC system used in research.



ATC alterations – splitting of groups

- Cephalosporins

  New classification according to generations in 2005 (four new ATC 4th levels, J01DB-J01DE) - old level deleted (J01DA)

- Immunosuppressants

  A split of the ATC group L04AA S*elective immunosuppresants* from 2008 and three new ATC 4th level was established*:*

  - *Tumor necrosis factor alpha (TNF-α) inhibitors* (L04AB)
  - *Interleukin inhibitors* (L04AC)
  - *Calcineurin inhibitors* (L04AD)

L04AA changed – gaps in ATC 5th level codes

Procedures for new ATC codes/DDDs and alterations

- All users can apply for new ATC/DDDs and alterations
- Requests should be addressed to the WHO Centre in Oslo
- New ATC/DDDs, alterations and objections to temporary ATC codes/DDDs are discussed and decided at the two annual meetings in the WHO Working Group
- ATC Index updated once annually, valid from January
  - New ATC codes, new DDDs and alterations implemented

Defined Daily Dose (DDD)

The DDD is the assumed

average maintenance dose per day for a

drug used for its

main indication in adults

The concept of the DDD

- A technical unit of measurement, represents an ”average” daily dose for the main indication
- Useful for measuring and comparing volume of drug use
- Should not be interpreted as the recommended or prescribed dose but as an international compromise based on review of available documentation

Drug exposure – expressed in DDDs

Is normally given as:

- **DDDs/1000 inhabitants/day**

Example: *10 DDDs/1000 inhabitants/day*

May indicate that 1% of the population can receive a certain treatment continuously (i.e. daily), *but this interpretation is only useful if there is good agreement with the average prescribed daily dose (PDD) and the DDD*

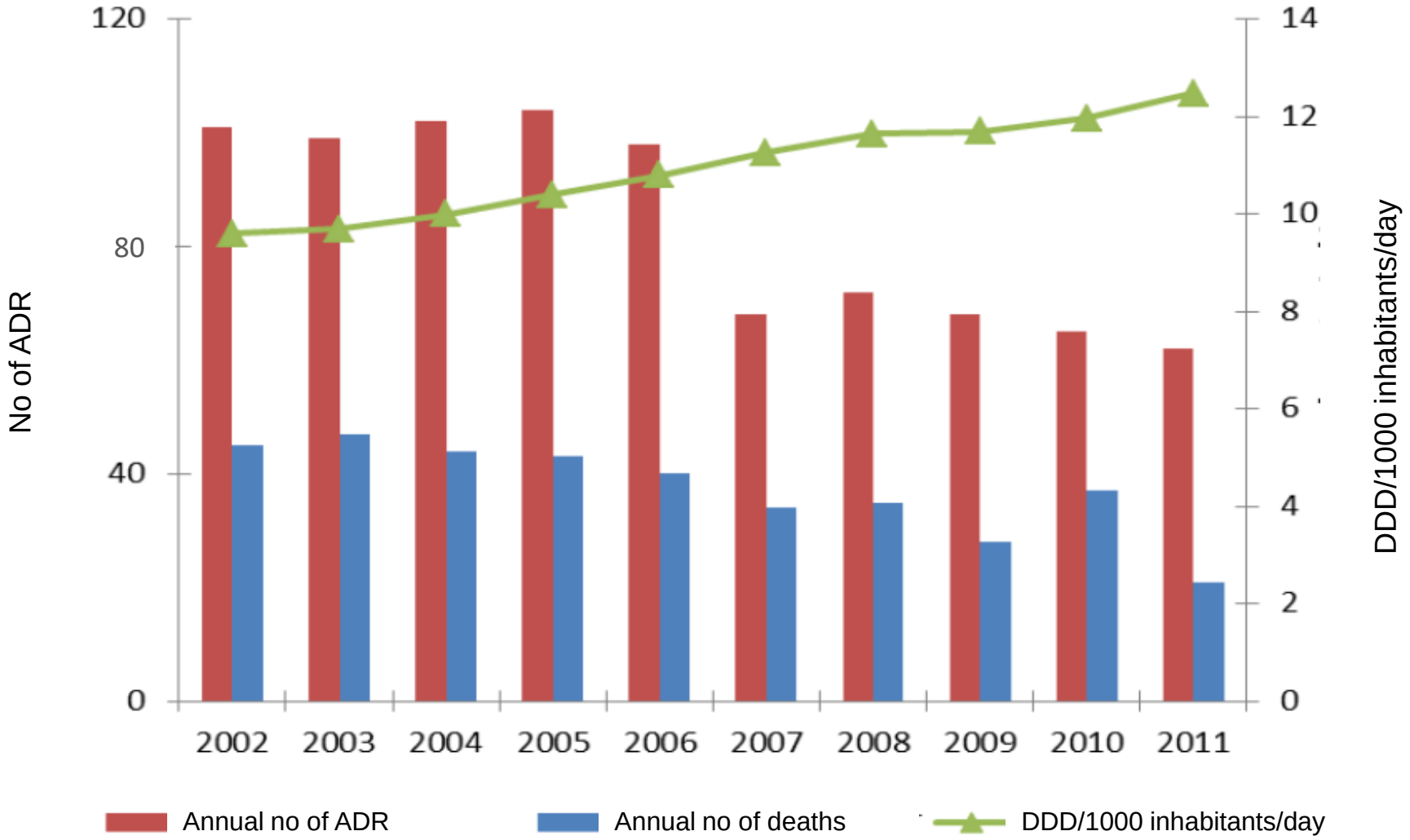
Used as surrogate for point prevalence (therapeutic intensity)

Applications of the ATC/DDD

Drug utilization and pharmacoepidemiology

- Pharmacovigilance
- Regulatory intervention and impact of drug use

Adverse drug reaction reports of warfarin (B01AA03) in Norway 2002-2011

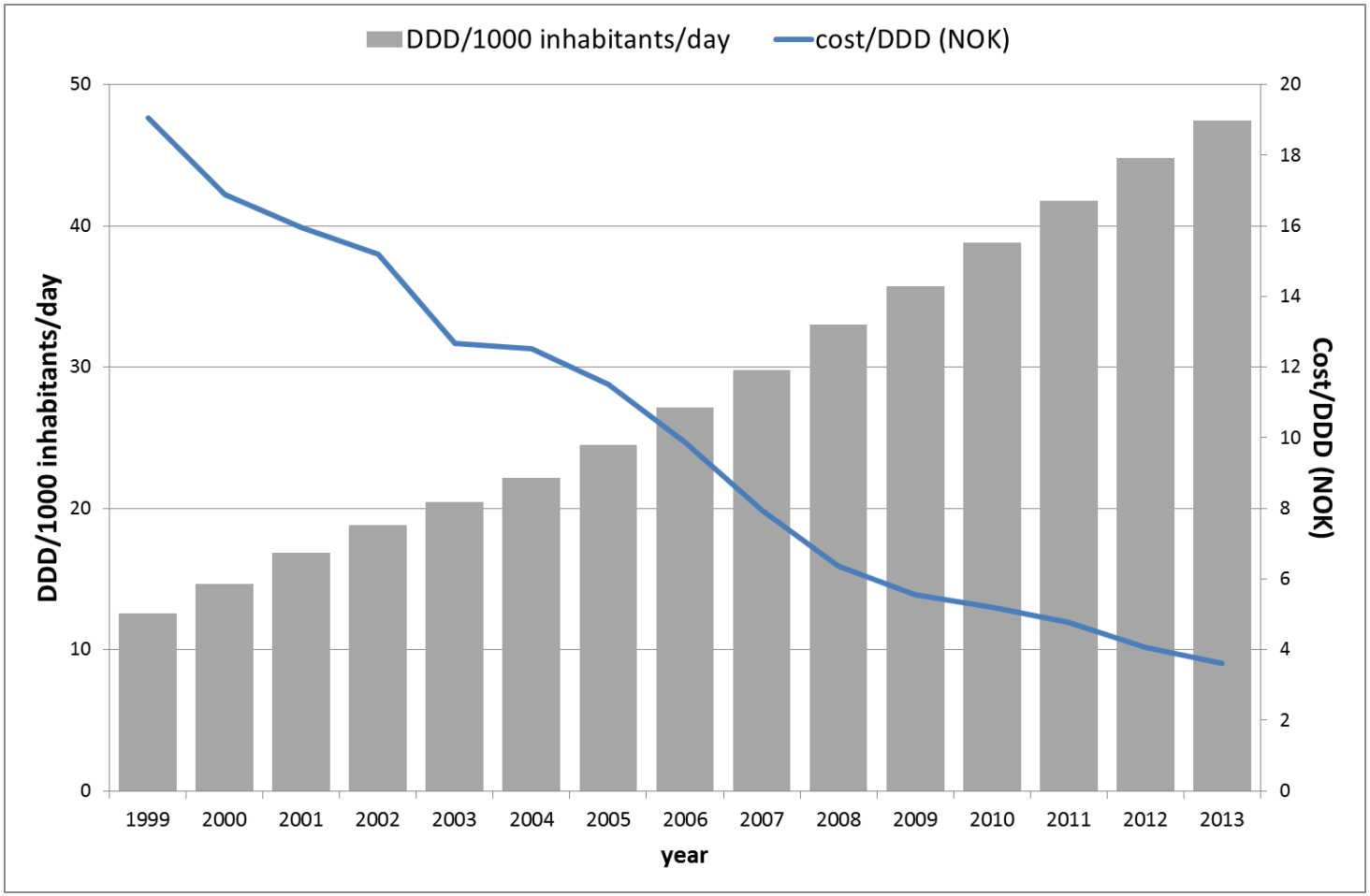


Source: Norwegian Medicines Agency, Annual report 2011

Monitoring drug expenditure

- ATC: to determine to what extent increased costs can be attributed to increased use of a drug group
- DDD: to compare costs of two formulations of the same active ingredient
- DDD: to follow the expenditure of a certain treatment

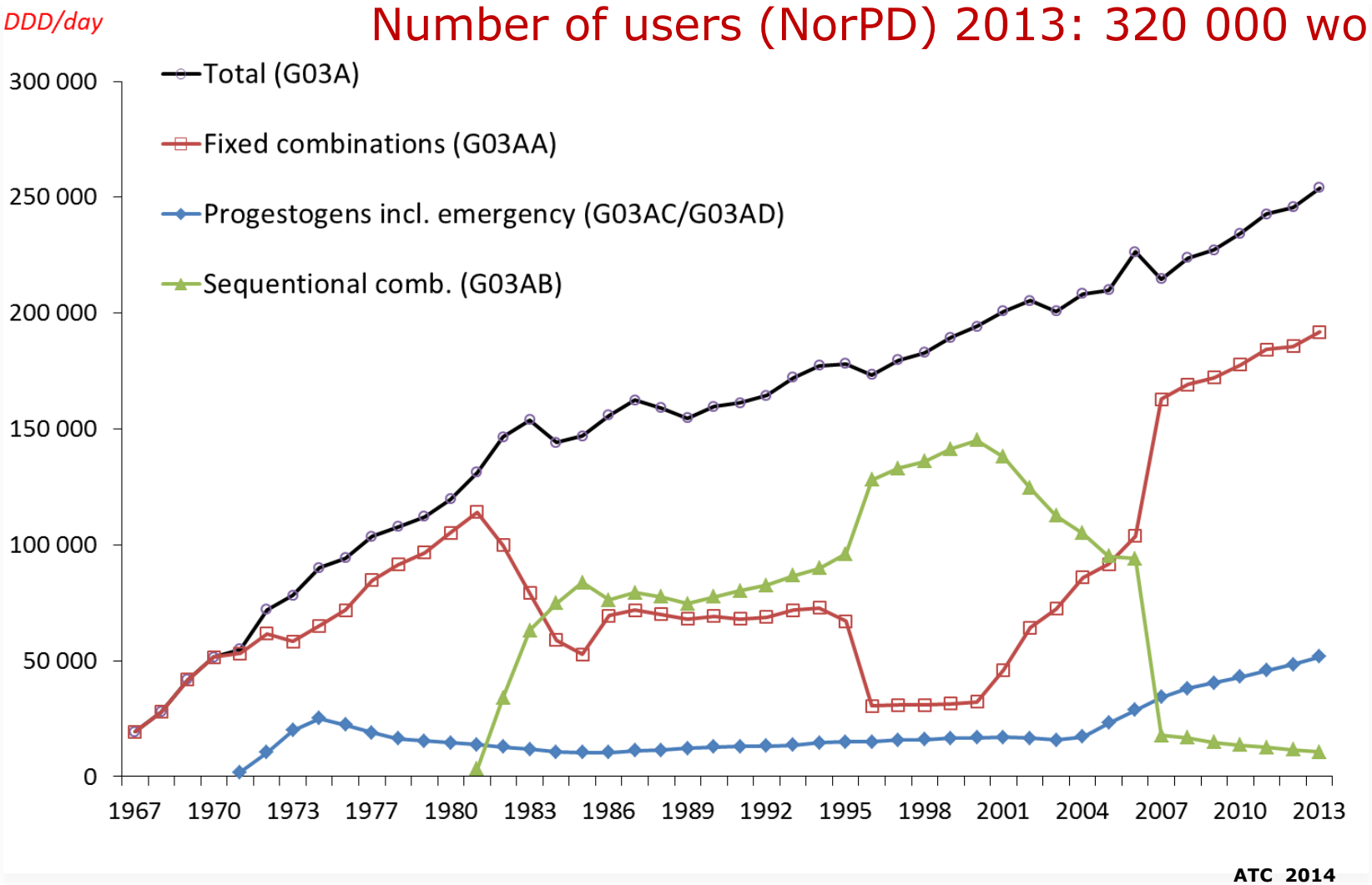
Sales of proton pump inhibitor (A02BC) in Norway 1999-2013



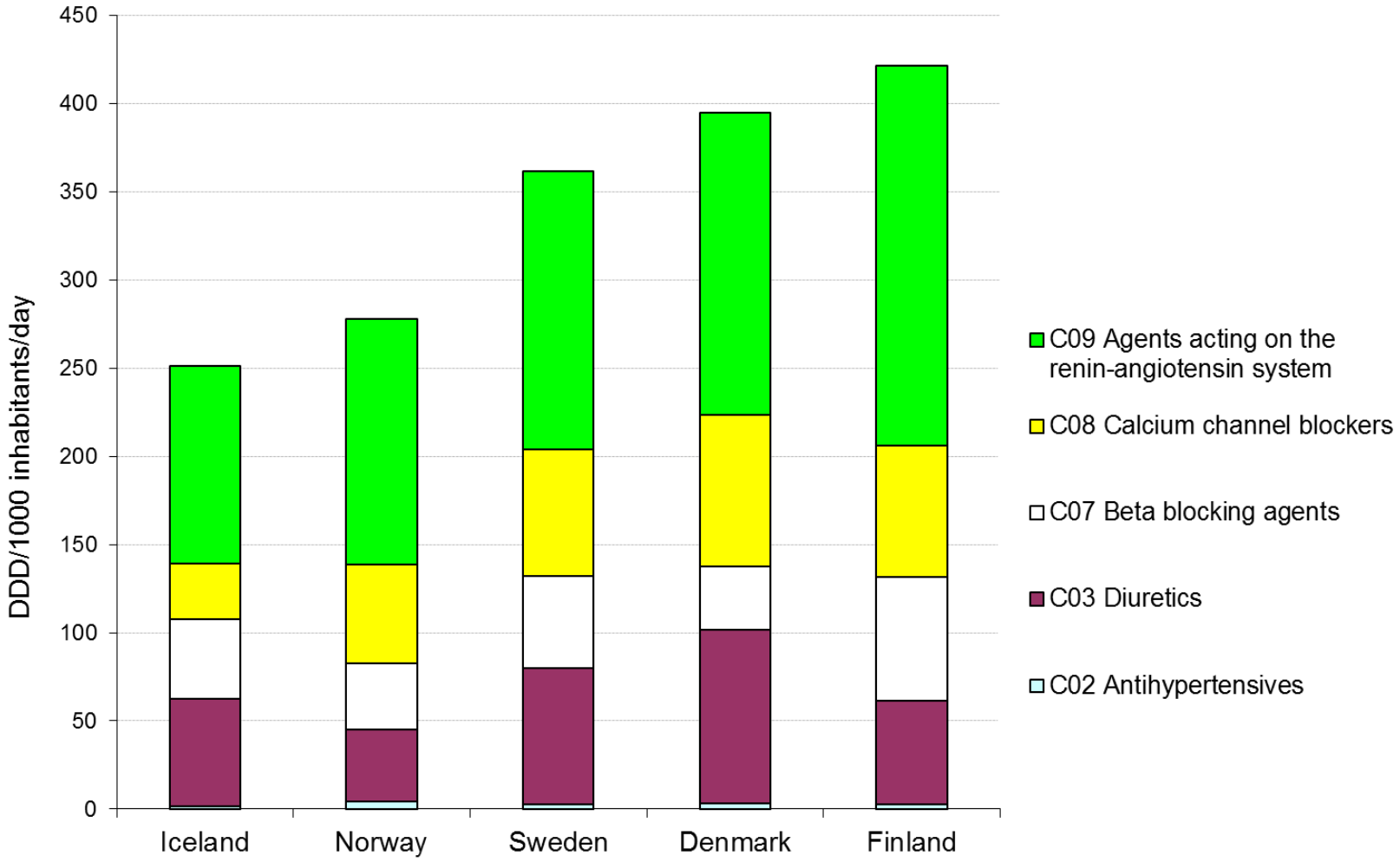
ATC 2014

Sales of contraceptives in Norway (ATC gr.G03A)1967-2013

(excl. IUDs, vaginal rings, implants and inj.)



Sales of agents used in e.g. hypertension in the Nordic countries in 2012



Source: Health statistics in the Nordic countries 2013, Nomesco

ATC 2013

Practical use in drug utilization…

Challenge:

- We provide a tool where ATC and DDD are established for active ingredient(s). The users have to make the correct link between the ATC/DDD value on the *medicinal product package level*.

ATC/DDD is a well established tool to:

- study patterns of use and changes over time
- evaluate the impact of information efforts, regulatory changes etc
- study drug exposure in relation to risk of adverse drug reactions
- indicate over-use, under-use and misuse/abuse of drugs
- compare and exchange data internationally

Proper knowledge about the ATC/DDD system is important

ATC/DDD Toolkit

for Drug Utilization Monitoring and Research

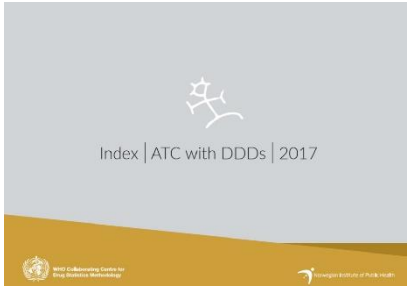
- Online resource for anyone interested in undertaking drug utilization studies
- Guidance on how to set up and use the international ATC/DDD methodology

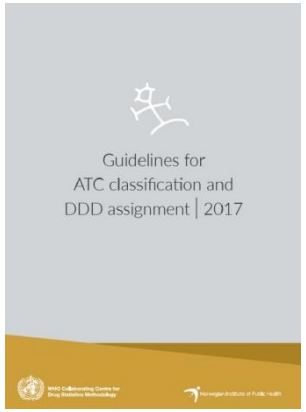
The Website for the Toolkit is developed and hosted by WHO Geneva

Went live March 2017: http://www.who.int/medicines/regulation/medicines-safety/toolkit/en/

ATC/DDD publications

- ATC Index with DDDs
- Guidelines for ATC classification and DDD assignment





Annually updated, and available in English and Spanish versions

Website

www.whocc.no