Why is (was?) there so low antibiotic resistance rate in Norway

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Take home messages

- There is (was) a low antibiotic (AB) resistance rate in Norway due to low antibiotic use

- But, bad things are happening!
  - total and broad spectrum AB use are increasing
  - resistance is emerging and spreading
  - No new antibiotics in the pipelines
Mortality rate USA 1900-2000.
Armstrong, JAMA 1999;281:61-6

Figure 2. Crude Mortality Rates for All Causes, Noninfectious Causes, and Infectious Diseases
Why concern about antibiotic resistance?

- AB-resistance is one of the biggest health problems (WHO)
- In EU 25,000 dies of AB-resistant microbes
- AB-resistance cost 55 bill. USD/year in USA
- 14,000 pts die from C. diff in USA/year
- No new ABs in the pipelines
Why do antibiotic use and resistance increase in Norway?

• AB-resistance increase because of
  ▫ Increasing total and broadspectrum antibiotic use
  ▫ AB use in animals (abroad)
  ▫ Globalisation (food import, tourism, refugees etc)
  ▫ Lack of infection control
Fleming A.

... the public will demand [penicillin]... then will begin an era... of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save.

In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism.

- I hope the evil can be averted.
History Teaches Us That Confronting Antibiotic Resistance Requires Stronger Global Collective Action
The Journal of Law, Medicine & Ethics 2015

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Dødeliget ved invasiv pneumokokkinf. 1929-35 Boston.
Thilgman & Finland. Arch Intern Med 1937

Chart 1.—Comparison of the incidence of bacteremia and the mortality for various age groups.
Aldersrelatert dødelighet ved S. aureus sepsis

Skinner D, Keefer CS. Arch Intern Med 1941
Bruk av antibiotika ved sykehus i Europa

Figure 3.19: Hospital use of antimicrobials for systemic use (ATC group J01) in the participating countries in 2008

- Penicillins (J01C)
- Cephalosporins and other beta-lactams (J01D)
- Tetracyclines (J01A)
- Macrolides, lincosamides and streptogramins (J01F)
- Quinolones (J01M)
- Sulfonamides and trimethoprim (J01E)
- Other J01 classes

DDD per 1000 inhabitants and per day

ESAC Yearbook 2008
Figure 5.3. *Streptococcus pneumoniae*, proportion of single erythromycin, single penicillin and dual resistance in 2004.
Figure 3.15. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2014.
Solution to Killer Superbug Found in Norway.
New York Times   December 30, 2009

OSLO, Norway (AP) -- Aker University Hospital is a dingy place to heal. The floors are streaked and scratched. A light layer of dust coats the blood pressure monitors. A faint stench of urine and bleach wafts from a pile of soiled bedsheets dropped in a corner.

Look closer, however, at a microscopic level, and this place is pristine. There is no sign of a dangerous and contagious staph infection that killed tens of thousands of patients in the most sophisticated hospitals of Europe, North America and Asia this year, soaring virtually unchecked.

The reason: Norwegians stopped taking so many drugs. Twenty-five years ago, Norwegians were also losing their lives to this bacteria. But Norway's public health system fought back with an aggressive program that made it the most infection-free country in the world. A key part of that program was cutting back severely on the use of antibiotics.
The use of antibiotics in pneumonia
Scan J Inf Dis 2002;34:56-60

Percent of courses

- Other
- Metronidazol
- Macrolide
- Aminoglycoside
- Cephalosporins
- Ampicillins
- Penicillin V & G
Cefalosporiner Aker og Tromsø
J Hosp Infect 2003, 54: 202-206
Adjust therapy according to blood cultures
JAC 2006;57:326-30

- **354 episodes** of positive blood cultures
  - **92 episodes** with CNS and other contaminants
    - **226 episodes** of true bacteraemia
      - Guidelines recommended adjustment of antibiotics in **166 episodes**
      - **Treatment adjusted in 146 (88%) episodes**
        - **Cost reduction 19800 EUR (21%)**
  - **In 36 episodes** the patients died or were discharged before the results of blood cultures
    - **Appropriate antibiotic therapy continued in 60 episodes**
Antibiotikabruk i Norge 1974-2014
Doseinflation in pneumonia
Medicinsk kompendium (Scandinavian “bible”)

- 1955  Penicillin 1.2 mill i.e
- 1969  Procain pen. 0.3 or pen V 0.2 x 4
- 1980  Pen G 1.0 followed by 0.3-0.5 x 4
- 1986  Pen G or V 1.0 x 2
- 1994  Pen G 5.0 followed by 2.0 x 3
- 2006  Aker Hospital 2.0 x 4
- 2002  Ullevål Hospital 5.0 x 3-4
Total antibiotikabruk i Norge
FIGURE 7. Sales for food-producing species, including horses, in mg/PCU, of the various veterinary antimicrobial classes, by country, for 2010. Differences between countries can partly be explained by differences in animal demographics, in the selection of antimicrobial agents and in dosage regimes, among other factors. *Amphenicols, cephalosporins, other quinolones and other antibacterials (classified as such in the ATCvet system).
Antibiotikabruk i fiskeoppdrett

Diagrammet viser bruk av antimikrobiale VMPs (tonn) og biomasse av slaktet fisk (1000 tonn) fra 1981 til 2011.
Tiltaksplan

Tiltak for å motvirke antibiotikaresistens (2000-2004)
So far, so good

- But, bad things are happening in hospitals
Increase in use of broad spectrum antibiotics in a large university hospital

Forbruk av utvalgte grupper antibiotika Haukeland Universitetssykehus 1992-2009 (DDD/100 liggedøgn)
Antibiotic use in eighth Norwegian hospitals 2002-07
Haug, JB et al JAC 2011 (core units)

Figure 1. Total consumption of antibiotics\textsuperscript{a} in core units\textsuperscript{b} of eight Norwegian hospitals (A–H) from 2002 to 2007 (DDD/100 BDs).
Resistensutvikling utvalgte agens/mekanismer
Isolater påvist ved Mikrobiologisk avdeling SiV

Antall pasienter

- E.coli ESBL
- MRSA
- Pseudomonas aeruginosa (meropenem I/R)
- Pneumokokker (penicillin I/R)
- E.coli AmpC
- Klebsiella pneumoniae ESBL

Graph showing the increase in isolates of different bacteria from 2005 to 2011.
Resistens E.coli Oslo og Norge 2013

![Graph showing the percentage of resistant E. coli isolates by antibiotic and hospital]
MRSA Norge

FIGURE 55. Reported cases of MRSA infections and colonisations in Norway 2006-2014, by healthcare associated (HA), community associated (CA) and imported cases.
So far, so good

- But, bad things are happening in general practice
- (85% of antibiotics are prescribed in general practice)

Figure 2. Distribution of 440 GPs’ antibiotic prescription rates for ARTIs.
Antibiotic use in norwegian nursing homes

Figure 1. Use of antibacterials in 133 nursing homes. Each column shows the use in 1 nursing home. ATC group J01 (excl. methenamine), P01 AB01 and A07 AA01 are shown in black and methenamine (ATC J01 XX05) in white. Use is measured in DDD/100 bed-d, ATC/DDD version 2004.
Conclusion

- Total AB use increased by 50% in 30 y
- Broad-spectrum use increases
- Doses increases
- Antibiotic resistance increases
- Surveillance is ok
- Guidelines must be actively implemented
The emerging problems in Norway

- ESBL-producing Gramnegatives are increasing
- MRSA
- Selection of other multiresistant bacteria
  - *Acinetobacter*
  - *Pseudomonas*
- Enterococci
  - Ampicillin resistant *E. faecium*
  - VRE (sporadic in Norway, epidemics in Sweden)
- Penicillinresistent pneumococci (PRSP)
  - Rare in Norway
What to do in Norway

- Follow national guidelines
- Bacteriological samples before AB
- Adjust therapy according to bacteriological findings
- Early switch to oral AB
- Shorten duration of therapy
- Use penicillin and aminoglycosides
- Prefer penicillins before cephalosporins
- Omit unnecessary ”double coverage”
Andre momenter

• Hvis AB er unødvendig; seponer umiddelbart!
• Seponer senest to dager etter at pas. er feberfri. Vi behandler for lenge!
• Lokalt virkende AB kan erstattes av antiseptika
• Diagnosen penicillinallergi er oftest feil
New antibiotics and development of resistance

Figure 1. Antibiotic introduction and the development of resistance Adapted from [3,4].

Norwegian guidelines for antibiotic use in general practice
FIGURE 18. Proportions of selected antibacterial agents for systemic use in Norwegian hospitals 2006-2014, measured in DDD/1,000 inhabitants/day.
Bruk av ciproxin og trend i ciprorseistente E.coli Norge

FIGURE 44. Usage of ciprofloxacin (blue) and prevalence of ciprofloxacin non-susceptibility in *Escherichia coli* blood culture isolates as defined by the 2015 breakpoints (orange) 2000-2014.
Resistance in blood isolates
EARSS 2008

MRSA Meticillinresistente gule stafylokokker

VRE - Vankomycin-resistente enterokokker
Figure 3.6. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2014

Legend:
- < 1%
- 1% to < 5%
- 5% to < 10%
- 10% to < 25%
- 25% to < 50%
- ≥ 50%
- No data reported or less than 10 isolates
- Not included

Non-visible countries:
- Liechtenstein
- Luxembourg
- Malta
Do we have enough guidelines? - or is it compliance the problem?

Statens helse-tilsyn 2001

Helse Vest 2005

Aker/SAB-2006

Helse Nord 2009

Primærhelse-tjenesten -2008
MRSA Europa 2014

Figure 3.23. *Staphylococcus aureus*. Percentage (%) of invasive isolates with resistance to meticillin (MRSA), by country, EU/EEA countries, 2014

- < 1%
- 1% to < 5%
- 5% to < 10%
- 10% to < 25%
- 25% to < 50%
- ≥ 50%
- No data reported or less than 10 isolates
- Not Included
CRP-itis

- CRP er uspesifikk
  - Vevsnekrose
  - Allergiske reaksjoner
  - Andre inflammasjoner

- CRP stiger sent og synker sent
  - Lav/normal CRP utelukker ikke akutt, alvorlig infeksjon
  - CRP-topunkt ofte etter at infeksjonen er under kontroll
  - Normalisering av CRP ikke nødvendig for å avslutte antibiotikabehandling

- Prokalsitonin
  - Mer spesifikk indikator på alvorlig bakteriell infeksjon
  - Kan og brukes til å avgjøre behandlingslengde/seponering
  - God vitenskapelig dokumentasjon (i motsetning til CRP)
  - Dyr test, evt. innføring må evalueres i fohold til mer disiplinert bruk av CRP og helst også antibiotikaforskriving
Farmakokinetikk penicillin pneumokokker
Dagan et al, JAC 2001;47:129-40

**Diagram:**
- **Penicillin concentration (µg/mL):**
  - 100
  - 10
  - 1
  - 0.1
  - 0.01
- **Time (h):**
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6

- **Dosage Levels:**
  - 24 million units/24h (by continuous infusion after loading dose)
  - 5 million units
  - 2.5 million units
  - 1 million units
  - 500,000 units

**Strain Susceptibility Classes:**
- **Highly-resistant strains (MIC ≥ 4.0 µg/mL)**
- **Intermediate-resistant strains (MIC ≤ 1.0 µg/mL)**
- **Susceptible strains (MIC ≤ 0.06 µg/mL)**
Guidelines in Norway
Tidsskr Nor Legeforen 2008; 128: 2335-9

- **Sepsis.** Penicillin + aminoglycoside
- **Pneumonia.** Penicillin 1,3 g x 4
  - With sepsis + gentamicin
  - Atypical erythromycin
- **Urosepsis.** Ampi + gentamicin
- **Cystitis.** Change between different AB
- **Skin & soft tissue.** Penicillin or kloxa/dikloxacillin
Aminoglycosides

- The most rapid acting antibiotic
- Bacterial killing proportional with top concentration
- Synergy with beta-lactams
- Side effect rare in short therapy
- No impact on normal bacterial flora
- Little resistance
- Dosing x1
Antibiotic susceptibility in respiratory tract pathogens

- Pneumococci, streptococci, and meningococci susceptible to penicillin
- *H. Influenzae* 10-15 % β-lactamase producers
- *Mycoplasma* susceptible to erythromycin
Treatment respiratory tract infections

- Community ac. pneumonia: Penicillin
- Nosocomial pneum: Pen. + aminoglycides or cefuroxime
- Atypical pneumonia: Erythromycin
- Tonsillitis/sinususitis: Penicillin
- Acute bronchitis: No antibiotics
- X-cerb chronic bronchitis: Antibiotics??
The choice of antibiotics in urinary tract infections

- **Cystitis**: Ampi, amoxcillin, mecillinam, nitrofurantoin, trimethoprim 3 days

- **Pyelonephritis**: Ampicillin + aminoglycoside, mecillinam, trimethoprim-sulfametoxazol

- Ciprofloxacin only for complicated UTI
Clostridium difficile

- Increased risk for *C.difficile* with use of broad spectrum antibiotics
- We do not know the frequency in Norway
  - 3. generation cephalosporins
  - Ciprofloxacin
    - Eks: ribotype 027 – increased virulence and mortality
  - Clindamycin
Deaths attributable to AMR every year compared to other major causes of death

AMR now 700,000 (low estimate)

- Tetanus 60,000
- Road traffic accidents 1.2 million
- Measles 130,000
- Diarrhoeal disease 1.4 million
- Cholera 100,000 – 120,000
- Cancer 8.2 million
- Diabetes 1.5 million

AMR in 2050 10 million
Fig. 1  Survival of patients with systemic pneumococcal infection according to the time after a positive blood culture for S. pneumoniae was drawn. Our material collected in Oslo, Norway 1993–1997 (excluding the children for comparability) compared to the study of Tilgham et al. collected in Boston 1929–1937 [15], Austrian et al. collected in New York State 1952–1962 [2] and Örtqvist et al. collected in Stockholm, Sweden 1977–1984 [13]. CFR (Final) case fatality rate.
Resistance in blood isolates
EARSS 2008

E. coli m ESBL

Klebsiella pneumonia m ESBL

KPC – karbepenem-resistente Klebsiella pneumonia
Barriers to guideline adherence

- Ignorance
- Awareness
- Familiarity
- Agreement
- Outcome expectancy
- Inertia of practice
- External barriers

Cabana MD. JAMA 1999; 282: 1458-65
Antibiotic use in Europe
Cars O et al. Lancet

Figure 3. Antibiotic prescription practice for ARTIs of 440 GPs by distribution of proportions prescribing non-pcV antibiotics.
Invasive pneumococcal infection after vaccination

*FIGURE 49.* Incidence rates of IPD caused by PCV-7. The vaccine was introduced in 2006.
Sales og macrolides and clindamycin
ANTIBIOTIC INTRODUCED

- 1943 penicillin
- 1950 tetracycline
- 1953 erythromycin
- 1960 methicillin
- 1967 gentamicin
- 1972 vancomycin
- 1985 imipenem and ceftazidime
- 1996 levofloxacin
- 2000 linezolid
- 2003 daptomycin
- 2010 ceftaroline
Aminoglykosides + penicillin is first choice in septicaemia in Scandinavia (also in neutropenic pts.)
Thorvaldsen M. Ugeskr Læger 2004;166: 2246-50

- **Norway:** First choice in 52/53 sykehus (JN Bruun, Tallin 2000)
- **Denmark:** 92% of intensive depts.
- **Sweden:** Often 2-3 doses aminoglycosides in sepsis
Impact of infectious diseases

- Average age has increased by 30 years/100 y
- 20 y because of better social standard
- 10 y because of medical progress of which 7 years are due to treatment/prevention of infections
First choice of antibiotics in Norway?

- Penicillin (ampicillin)
- Gentamycin
- Metronidazol
- Kloxa/dikloxacillin
- Erytromycin
- Cefuroxim
På Aker behøver vi 6 antibiotika

- Penicillin (ampicillin)
- Gentamycin
- Metronidazol (Flagyl)
- Dikloxacillin (Diclosil)
- Erytromycin
- Cefuroxim (Lifurox)

Alle andre er sekundærvælg
Use of macrolides in Finland

**Figure 1.** Total Consumption of Macrolide Antibiotics by Outpatients in Finland from 1976 through 1995. Consumption is expressed in terms of defined daily doses per 1000 inhabitants per day.
Reversal of macrolide resistance

**Figure 2.** Frequency of Resistance to Erythromycin among Group A Streptococcal Isolates from Throat-Swab and Pus Samples in Finland in 1990 and in 1992 through 1996. The data from 1990, obtained from six regional microbiology laboratories, are shown here for comparison; the dashed line indicates that the 1990 data were not included in the statistical analyses reported in the text.
Flemmings advarsel mot overforbruk av penicillin

"The public will demand [the drug and]…then will begin an era…of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals… In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope the evil can be averted."
Confucius 551-479 B.C.

• No country can afford not to have an antibiotic policy
Topics to be discussed

- Trends in antibiotic use
- Trends in antibiotic resistance
- Issues to improve antibiotic use
Økende bruk av karbapenemer

Tienam®, Meronem®, Invanz®

- 3. håndsmidler, bør reserveres for infeksjoner der første- og andrehåndsmidler ikke kan brukes

- Som empirisk behandling bare til alvorlig syke pasienter der det er risiko for infeksjon med særlig resistente bakterier (ESBL-produserende og andre)
  - Må kjenne lokale resistensforhold, dvs hvor hyppig ESBL-produserende bakterier forekommer blant egne pasienter
Forbruk av fluorokinoloner ved kirurgiske avdelinger, Aker universitetssykehus

Definerte døgndoser (DDD)

- Urologisk avd.
- Karkirurgisk avd.
- Gastrokir. avd.
- Ortopedisk avd.
Use of clindamycin and carbapenem Aker and Tromsø.
Berild D, Ringertz SH. J Hosp Infect 2003; 54:202-6
Resitance in S. aureus

Sales of penicillin
Figure 3.19: Hospital use of antimicrobials for systemic use (ATC group J01) in the participating countries in 2008

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- Other J01 classes

DDD per 1000 inhabitants and per day

Countries: FI, LV, IT, FR, LU, EE, BE, RU, SK, DK, NO, SI, IE, BG, SE, HR, MT, HU, IL

ESAC Yearbook 2008
Broad spectrum antibiotic use in Norwegian hospitals

![Graph showing the use of different antibiotics by DDD/1000 inhabitants/day from 2000 to 2009.](Addis Ababa 2012)
Antibiotika brukt ved luftveisinfeksjoner

- Beta lactamase sensitive penicillins (J01CE)
- Penicillins with extended spectrum (J01CA) excl. pivmecillinam
- Tetracyclines (J01A)
- Macrolides and lincosamides (J01F)

High incidence of influenza

- Amoxicillin introduced
- Azithromycin and clarithromycin introduced
- Abolishment of the need clause
- Norwegian national plan to combat microbial AB resistance
- National Guidelines AB use in ambulatory care
- Lyme-borreliose
- Copenhagen EU-Conference on the Microbial Treat
- Addis Ababa 2012