

Report from the ECDC Visit in Denmark to Discuss Antimicrobial Resistance, 12-16 January 2009

Observations

Antimicrobial resistance (AMR) and antimicrobial consumption in Denmark

The situation in Denmark about AMR and antibiotic use has been and still is more favourable compared to most EU Member States. There is large group of professionals with expertise in the field of AMR. Denmark was at the forefront of establishing an integrated approach for surveillance of AMR and antibiotic use, both in humans and in the food chain, and publishing the results in a yearly DANMAP report.

However, recent national data from DANMAP as well as local data indicate that antibiotic use in humans is increasing, both in outpatients and in hospitals, and there have been, and currently are, several outbreaks due to multidrug-resistant bacteria.

National coordination

There are many relevant players in the field of AMR who know each other and, to some extent, interact with each other. These players have met under various groups such as the DANMAP Board where Statens Serum Institut, the Danish Medicines Agency, National Food Institute- Technical University of Denmark and the Danish Food and Veterinary Administration are represented. However, the DANMAP Board does not cover all aspects of AMR, in particular the management of AMR in other bacterial diseases than foodborne. Additionally, the DANMAP Board has not produced a national strategy for management of AMR. It therefore does not represent an Intersectoral Coordination Mechanism (ICM) as stated in Council Recommendation 2002/77/EC.

The Ministry of Health and Prevention has held several intersectoral meetings with a larger number of stakeholders: Statens Serum Institut, the National Board of Health, the Danish Medicines Agency, the Institute for Rational Pharmacotherapy and the Danish Veterinary and Food Administration, National Food Institute-Technical University of Denmark. There are no formal conclusions of these intersectoral meetings and discussions are currently on-going.

Organized multidisciplinary and multisectoral collaboration on local level

There has recently been a major reform where the country has been reduced to 5 regions and 98 municipalities. Since 2007, the regions organise health services and are responsible for hospitals and doctors. There are regional coordinating groups focusing on AMR (e.g. MRSA), medicines (incl. antibiotic use) and infection control. These groups, however, were recently implemented, or are in the process of being implemented, and are not present in all regions.

In hospitals, there are different groups for different areas (e.g., medicines, infection control). Interaction between microbiology diagnostics, guidance for antibiotic therapy and infection

control is facilitated by the fact that infection control is part of the clinical microbiology department and guidance for antibiotic therapy is often provided by clinical microbiologists.

Laboratory capacity

There is a high level of microbiology laboratory capacity, with several clinical microbiologists in each laboratory. There is a reference laboratory for AMR at Statens Serum Institut.

There is no national external quality assessment scheme. Most laboratories participate in the external quality assessment organised by NEQAS and in EQA in conjunction with EARSS. In general, preliminary microbiology results can be provided within 24 hours of receipt of the specimen.

General practitioners submit clinical specimens for microbiological investigation.

Monitoring of antibiotic resistance

A selected number of AMR indicator bacteria have been surveyed by DANMAP. Fourteen out of 15 clinical microbiology laboratories report data to DANMAP.

AMR data have gradually been reported by the Danish Study Group for Antimicrobial Resistance Surveillance (DANRES) to EARSS. Fourteen clinical microbiology laboratories in DANRES report data to EARSS. More detailed data are available at the local/hospital level and at the reference laboratories at Statens Serum Institut.

AMR surveillance is not uniform. Reporting of electronic laboratory AMR data is not compulsory. Notification of MRSA cases is compulsory. However, notification is not compulsory for other AMR bacteria, e.g. extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* or vancomycin-resistant enterococci (VRE), and not all labs submit isolates to the AMR reference laboratory.

Data on AMR by main focus of infection (other than blood and urine) are available at local/hospital level, but are not reported by DANRES or DANMAP.

Monitoring of antibiotic usage

For human medicine, data on antibiotic packages dispensed at the country's pharmacies are collected by the Danish Medicines Agency since 1994 for outpatients and since 1997 for hospitals. These data are reported in the DANMAP report, in a yearly national report on the use of medicines and on the website of the Danish Medicines Agency (Medstat, Ordiprax for community doctors). Community data are available at the dispensation (prescription) and patient level, but hospital data are only available at the department level.

Limitations for a more detailed analysis of these data for antibiotic management and intervention purposes are: the lack of information on the individual prescriber and the lack of information on clinical diagnosis or indication for prescription (both in the community and in hospitals).

On the local level, there are differences in the detail of collected data and timeliness of analysing these data on antibiotic consumption.

For veterinary medicine, data on antibiotic use are available since 1994. Since 2001, antibiotic prescriptions to animals redeemed at pharmacies, including animal species, broad disease category, farm identifier, prescriber identification are reported to VetStat. These data are analysed and reported to DANMAP.

Antibiotic utilization and treatment guidance

Antibiotics cannot be obtained without a doctor's prescription.

There are national guidelines written by a group composed of selected members of professional societies (clinical microbiologists, infectious disease specialists, general practitioners) and published in the drug compendium and on the web portal Medicin.dk. The Institute for Rational Pharmacotherapy is recommending certain antibiotics as drug of choice and alternative for various bacterial diseases. The National Board of Health has produced guidelines for treatment of sexually transmitted diseases. There are many local guidelines at hospital level, which include clinical guidance and recommendations on when and how to take clinical samples. At regional level and with the aim of saving costs, there are lists of recommended antibiotic commercial names.

There is no sustained monitoring of compliance with guidelines. Although within the regions, feed-back is provided to prescribers on their prescriptions, the focus is more on choice of the cheapest equivalent medicine (to save money) rather than compliance with guidelines and rational use (that could contribute to prevent AMR).

The regional pharmaceutical consultants are responsible for providing audit and guidance for prescriptions of medicines. Focus of these activities on antibiotics varies depending on the region.

Most general practitioners participate in peer discussion groups and have, at least once, participated in a prescription audit organised by the Audit Projekt Odense (APO). Interventions organised by APO have shown their success in improving antibiotic prescriptions by GPs.

Infection control

There are infection control teams (doctors, nurses) and the standards of infection control in Danish hospitals are high.

Since 2008, there is an infection control committee at national level (Standing Hygiene Committee).

At regional level, strategic boards for infection control are being implemented.

There are infection control committees in hospitals.

The hospitals that we visited did not have continuous monitoring of healthcare-associated infections, although one hospital is starting a project in this area.

Alcohol-based solutions for hand hygiene were available in all visited hospital wards.

National MRSA guidance was produced following the increase in MRSA in the country. A specific regional MRSA competence centre recently opened in the Capital Region. Implementation of such regional coordination units is recommended in the national guidelines to prevent spread of MRSA.

In municipalities, there is no organised infection control structure. In general, the hospital infection control team is not involved in community infection control issues. In a few places, there is collaboration between municipality and hospital infection control staff (e.g. MRSA competence centre), but these are rare exceptions.

Educational programs on AMR

There are education courses on antibiotic treatment organised for qualification as a medical specialist. These antibiotic courses are compulsory.

In Denmark, clinical microbiologists have a central role in hospital antibiotic policy and consulting, but the current education programme of young microbiologists, may not include sufficient clinical training for performing these tasks. The training of young microbiologists is now shorter and, in particular, does not anymore include training at an infectious disease department.

There are post-graduate courses on antibiotic usage organised by the regions. In one hospital that we visited, there was a mandatory short introduction course on AMR and antibiotic usage.

For veterinarians, there are only courses on how to use antibiotics to treat animals, but no education on the prudent use of antibiotics to limit AMR.

Public information related to AMR

There seems to be a good knowledge about antibiotics in the general population. Limited evidence suggests that there is not widespread, unwarranted patient demand for antibiotics. Nevertheless, the Ministry of Health and Prevention has produced a leaflet entitled "Antibiotics. Only when it is necessary". On 18 November 2008, a scientific conference was organised and a press release was produced for European Antibiotic Awareness Day.

Denmark is participating in the European Commission (DG SANCO)-financed e-Bug project to educate school children on antibiotics and hygiene.

Marketing related issues

In Denmark, EU Pharmaceutical Directive 2001/83/EC is followed. There is a board representing prescribers and the pharmaceutical industry to deal with marketing practices: *Nævnet for Selvjustits på Lægemiddelområdet*. Independent information on antibiotics is available from the Institute for rational Pharmacotherapy. Additionally, there is a regional pharmaceutical consultant in each region.

Conclusion

Internationally, it is widely accepted that AMR is increasing and is a major concern all over the EU.

It is widely accepted that AMR is associated with antibiotic usage. Moreover, spread of AMR strains also takes place in hospitals through transfer of patients, population and foods in the country and across borders.

In Denmark, it seems that AMR in common clinically-relevant microorganisms is increasing. Antibiotic usage is also increasing and this is only partly explained by increasing daily dosages and ageing of the population.

It is disturbing to see the large discrepancy between the various views of Danish experts on the AMR situation in the country. The AMR and antibiotic use changes in Denmark, as well as the seriousness of the current AMR situation, have been questioned by leading antibiotic experts at one university hospital in contrast with what the analyses of other experts in Denmark have concluded. This sends a confusing message about the AMR and antibiotic use situation in Denmark.

Suggestions

There is an urgent need to create a specific intersectoral coordinating group (ICM) with a mandate to act and to develop a process involving all stakeholders based on a common understanding of the current situation of AMR development in Denmark. As a first step of this process, a national plan should be developed. The plan should clearly define mandates, responsibilities, tasks and be adequately funded. The present situation clearly suggests that the coordination responsibility should reside within the branch of government responsible for risk management. Adequate resources are needed to fulfil this task. However, the amount of money necessary for this coordination is limited. The experience of some EU countries, e.g. Belgium, France, shows that money can be saved by implementing actions to control and prevent unnecessary antibiotic use and AMR.

As part of this plan, a detailed analysis of all available data will need to be performed. Despite of the wealth of AMR and antibiotic use data available in the country, additional data such as diagnosis for each antibiotic prescription and unequivocal identification of individual prescribers will be needed to understand the increase of antibiotic prescribing in Denmark.

Due to its leading position in the field of human-veterinary interaction leading to AMR, Denmark should take on the task of further investigating the role of animal antibiotic exposure for human health to clarify the interplay between the human and veterinary sector. Examples where this interplay needs to be clarified is ESBL-producing *Escherichia coli* and livestock-associated (associated mainly with pig production) MRSA. This is an issue for the whole EU, in particular the situation in the Netherlands is comparable to that of Denmark. European and international collaboration should be encouraged and would also benefit Denmark.

Due to the existing organisation of its healthcare system, Denmark should seize the opportunity to further develop models for integrated funding of preventive measures, diagnostics and treatment that would, e.g., facilitate prevention and control of AMR. The fact that municipalities share the costs of patient hospitalisations may be a step in this direction.

In the light of increasing use of broad-spectrum antibiotics in hospitals, restrictive measures by whom and when these antibiotics can be used should be considered.

Further development of more rapid, point-of-care tests for the diagnostic of infections and for orienting antibiotic therapy is needed.

Lessons for other countries

Denmark was the first country to produce a yearly, integrated report - DANMAP - on the analysis of AMR and antibiotic use in human and veterinary medicine (food animals and foods). A few other countries have started to produce similar reports. The DANMAP report still serves as a model for other countries.

Audit Projekt Odense (APO) and its extension to a few other EU countries through funding by DG Research of the European Commission (HAPPY AUDIT) is an example for other countries of how the practice of prescribing antibiotics in outpatients can be improved through regular audits and feed-back of individual to prescribers.

Annex 1 - Team

Dr. Dominique L. Monnet, ECDC, Stockholm, Sweden

Dr. Peet Tüll, Visby, Sweden

Prof. Milan Cizman, Ljubljana, Slovenia

Dr. Gunnar Skov Simonsen, NORM, University Hospital of North Norway, Tromsø, Norway

Annex 2 – Persons met

Monday 2009-01-12

Meeting at National Board of Health, Copenhagen

- Dorthe Søndergaard, Anna Skat Nielsen (Ministry of Health and Prevention)

- Tove Rønne, Annemarie Knigge (National Board of Health)

- Jan Poulsen (Danish Medicines Agency)

Presentations at Statens Serum Institut, Copenhagen

Welcome

- Niels Frimodt-Møller (Statens Serum Institut)

Introduction to DANMAP and its organisation

- Anette M. Hammerum (Statens Serum Institut)

Veterinary antimicrobial consumption

- Vibeke Frøkjær Jensen (National Food Institute, Technical University of Denmark)

Monitoring antimicrobial resistance in zoonotic and indicator bacteria from animals and humans

- Hanne-Dorthe Emborg (National Food Institute, Technical University of Denmark)

Monitoring antimicrobial resistance in bacteria from food

- Justin C. Ajufu (Danish Veterinary and Food Administration)

Human antimicrobial consumption

- Ulrich Stab Jensen (Statens Serum Institut)

Monitoring of antimicrobial resistance in human pathogens including *E. coli*, streptococci, *S. aureus* and enterococci

- Anette M. Hammerum (Statens Serum Institut)

Also present: Line Skjøt-Rasmussen, Stefan S. Olsen (Statens Serum Institut), Frank M. Aarestrup (National Food Institute, Technical University of Denmark)

Tuesday 2009-01-13

Presentations at Danish Medicines Agency, Copenhagen

- **Organisation: Danish Medicines Agency and Institute for Rational Pharmacotherapy**
- **The Register of Medicinal Product Statistics**
- **National List of Recommendations**
- **Consumption of antibiotics: Denmark vs. Europe**
- **Courses and interventions**
- **Consumption analysis for use of broad-spectrum antibiotics**
- **Publications**
- **Changes in total antibiotic consumption 2007 to 2008**
- **Ordiprax (tool for benchmarking GP prescriptions of medicines)**

- Jan Poulsen, Søren Kristensen (Danish Medicines Agency)
- Tenna Bekker (Institute of Rational Pharmacotherapy)

Presentations at Danish Veterinary and Food Administration, Søborg

The Danish risk management strategy for veterinary antimicrobial usage

- Annette Cleveland Nielsen, Special Veterinary Advisor

Managing antimicrobial resistance in bacteria from food and food animals

- Justin C. Ajufu, Veterinary Officer

Also present: Thomas Lund Nielsen, Veterinary Officer

Meeting at National Food Institute, Technical University of Denmark, Søborg

- Henrik C. Wegener, Director

Wednesday 2009-01-14

Presentations and visit of Aarhus University Hospital, Skejby

Clinical microbiology and infection control

Clinical microbiology in Central Denmark Region (Midtjylland)

- Jens K. Møller, Associate Professor and Senior consultant microbiologist

The Drug Committee of Aarhus University Hospital and the new Regional Drug Committee

- Inge Vand, hospital pharmacist

Infection control organisation in Central Denmark Region (Midtjylland)

- Brian Kristensen, Senior consultant microbiologist

HAIR: automated surveillance of hospital infections

Not presented due to lack of time.

Also present: Svend Ellermann-Eriksen, Head of Department and Senior consultant microbiologist; Elisabeth Lund, Infection control nurse; Rita Andersen Leth, Surveillance manager; Dept. of Clinical Microbiology. Jette Lyngholm Nielsen, Hospital pharmacist.

Visit of intensive care unit, Aarhus University Hospital, Skejby

- Mads Holmen Andersen, ICU consultant

Presentations at University of Southern Denmark, Odense

Happy Audit (Health Alliance for Prudent Prescribing, Yield And Use of anti-microbial Drugs In the Treatment of Respiratory Tract Infections)

- Lars Bjærrum, Ass. Professor, Research Unit of General Practice

Happy Audit: Quality indicators for diagnosis and treatment of respiratory tract infections in general practice

- Malene Plejdrup Hansen, M.D., Ph.D. student, Research Unit of General Practice

Rational prescribing in Region Zealand

- Kirsten Schæfer, Pharmaceutical Consultant, Region Zealand

Audit on respiratory infections according to the APO-method, January 2009

- Anders Munk, General Practitioner, Director of Audit Projekt Odense, Research Unit of General Practice

Also present: Jens Damsgaard, General Practitioner, Hvalsø

Thursday 2009-01-15

Presentations and visit of Hvidovre Hospital, Hvidovre (Capital Region)

Clinical microbiology and infection control

- Bettina Lundgren, Head of Department
- Jenny Dahl Knudsen, Consultant microbiologist
- Henrik Westh, Consultant microbiologist
- Rie Mikkelsen, Infection control nurse

Visit of infectious disease department

- Gitte Kronborg, Infectious disease consultant

Lunch and discussion with:

Torben Mogensen, Medical Director

Meeting at Rigshospitalet-Copenhagen University Hospital (Capital Region)

Clinical microbiology and infection control

- Niels Høiby, Professor, Chairman of Department
- Michael Tvede, Head of Department
- Leif Percival Andersen, Infection control consultant

Friday 2009-01-16

Preliminary report from ECDC at National Board of Health

- Anna Skat Nielsen (Ministry of Health and Prevention)
- Tove Rønne, Sigrød Poulsen (National Board of Health)
- Niels Frimodt-Møller, Anette M. Hammerum (Statens Serum Institut)
- Jan Poulsen, Søren Kristensen (Danish Medicines Agency)
- Tenna Bekker (Institute of Rational Pharmacotherapy)
- Jenny Dahl Knudsen (Dept. Clinical Microbiology, Hvidovre Hospital)
- Brian Kristensen (Dept of Clinical Microbiology, Skejby Hospital)
- Henrik C. Wegener (National Food Institute, Technical University of Denmark)