

Title: Use of antimicrobials and occurrence of resistance in organic cattle herds

Acronym: Resistance in organic farming

Date: 24/2-00

1. Summary

Organic farming is among other things characterised by a more restrictive use of antimicrobial agents. A low occurrence of antimicrobial resistance can be regarded as a sign of quality. However, to be acceptable a limited use of antimicrobial agents has to be without adverse negative effect on animal welfare to be acceptable. In this study methods to perform a continuous surveillance for antimicrobial resistance at herd level will be used to compare the occurrence of resistance between organic and conventional dairy herds. In addition the treatment pattern of animals in organic herds will be studied. Based upon this information guidelines for disease treatment will be developed and implemented as herd specific treatment strategies which meet the demand for animal welfare and minimises the risk for antimicrobial resistance.

2. Research group

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3. Introduction

Organic farming is among other things characterised by a more restrictive use of antimicrobial agents. There is no evidence to suggest that the types of bacteria infecting organic herds are different from those causing problems in conventional farming. However, preliminary results from poultry and cattle production indicate that the occurrence of antimicrobial resistance is lower in organic herds compared to conventional (Aarestrup 1998, Aarestrup et al. unpublished).

A low occurrence of antimicrobial resistance can be regarded as a sign of quality. If antimicrobial resistance in the future should be a parameter of quality of organic products, it is essential that it is possible to detect a significant difference and that it is feasible continuously to monitor the occurrence of resistance at the herd level.

A restrictive use of antimicrobial agents is expected to have a beneficial effect by a lower occurrence of antimicrobial resistance. However, a restrictive use of antimicrobial agents may also have a negative impact on animal welfare if diseased animals are not treated. Beside the pain and distress experienced by the diseased animal, the result of insufficient treatments could be an increased occurrence of infections on herd level, and consequently also higher burden of infection.

4. State of the art

The greatest threat to the effective use of antimicrobial agents for therapy of bacterial infections is the development of resistance in pathogenic bacteria. Bacteria isolated from patients before antibiotics came into clinical use had virtually no resistance genes (Hudges & Datta 1983), but already shortly after the introduction of antimicrobial agents for therapy, the first resistant bacteria emerged (Levy 1982). It is generally accepted that there is a close relationship between the use of antimicrobial agents and the occurrence of resistance (Aarestrup 1999). However, only a limited number of studies have determined the association between the occurrence of resistance and use of antimicrobial agents at the herd level.

Escherichia coli have been suggested as indicator organisms to be isolated from healthy animals in relation to continuous surveillance programmes and epidemiological studies on antimicrobial resistance (Aarestrup et al. 1998).

As bacterial populations undergo dynamic processes and numbers may undergo considerable changes over time it is needed to determine the dynamics over time and the influence on the outcome of a continuous monitoring system.

The extended slaughter and milk withdrawal period following treatment in organic farming make alternative approaches to disease control more attractive. This must be expected to influence the treatment strategy in each herd during the conversion procedure from conventional to organic (Vaarst 1995, Vartdal & Blekesaune 1992). A low level of use of antibiotics in treatment of acute clinical mastitis was observed in Danish organic farms in early 90-ties (Vaarst 1995). The restricted use of antibiotics did not result in more clinical cases or in subclinical infections and in general, the udder health on organic farms was comparable or even better than on conventional farms (Vaarst 1995). Internationally there is a strong pressure against a more limited use of antimicrobial agents (WHO 1997). However, it is very important to ensure that a more limited use of antimicrobial agents is not accompanied by less welfare.

5. Objectives and expected achievements

Objectives and tasks

- To determine potential differences in the occurrence of antimicrobial resistance between conventional and organic dairy farms
- To investigate the possibility to perform a continuous monitoring of antimicrobial resistance by evaluating the dynamics of antimicrobial resistance.

- To characterise the treatment pattern of organic herds and based on this, develop guidelines for disease treatment which fits the goals for the organic herd, meet the demand for animal welfare and minimise the risk for antimicrobial resistance.

6. Description of workpackages including methods

Table 1: Workpackage list

Work-package No	Work package title	Responsible participant	Budget	Start	End	Deliverable No
1	Monitoring of use of medicine	SMT	225	1	33	1
2	Occurrence and dynamics of antimicrobial resistance in dairy herds	FAA	825	12	39	3, 6, 8
3	Characterization of treatments in organic farms	MV	305	7	39	5, 9
4	Use of herd specific plans for control of antibiotic resistance	SMT	248	10	39	9, 10

WP1: Monitoring of use of medicine

Workpackage number:	1
Start date or starting event:	1 st month (05-2000)
Responsible person:	SMT
Contributing persons:	TWB MV
Person-months: Scient.	2½ 0
Tech.	3½

Objectives

- To provide data on the use of drugs and clinical cases of mastitis in participating dairy herds.

Description of work

A registration and reporting procedure on the use of drugs for individual animals will be established in a way that makes comparison among herds valid.

From the Danish cattle database registrations of production and somatic cell counts will be available.

Clinical cases of mastitis will be described using a protocol which is being developed by the research group in other ongoing projects.

Deliverables

1. Data on disease, use of medicine and clinical cases of mastitis for use in WP2, WP3 and WP4

Milestones

- M3 Establishment of a system for registration of use of drugs and disease in herds
M4 Introduction of registration of clinical cases of mastitis
M13 Termination of data collection

WP2: Occurrence and dynamics of antimicrobial resistance in dairy herds
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Workpackage number:	2	
Start date or starting event:	06-2001	
Responsible person:		FAA
Contributing persons:	TWB/ SMT	FAA
Person-months: Scient.	4	2
Tech.		19

Objectives

- To compare the occurrence of antimicrobial resistance in organic and conventional dairy herds.
- To follow the dynamics of antimicrobial resistance over time and in relation to disease treatment

Description of work

Sampling and laboratory analysis

Antimicrobial resistance will be evaluated in 10 old organics herds, which have been delivering organic milk for at least 5 year and 10 herds which started delivering organic milk in 1999. Samples will be taken from 10 calves and 10 cows. Sampling will take place medio 2001 and primo 2003.

The occurrence of antimicrobial resistance will be followed among *E.coli* in 5 of the organic herds. Samples will be taken from 10 cows and 10 calves every 3 month over 1 year. Furthermore, the occurrence of antimicrobial resistance in animals receiving treatment will be followed.

For comparison data from 20 conventional herds from 2000 and from the herds converting to organic farming in 1999 will be available through another project performed by the research group.

E. coli will be isolated from the samples using standard procedures at DVL. One colony from each sample will be chosen for MIC determination. MIC determinations will be performed using a commercially prepared dehydrated panel (Sensititre).

Data analysis

Differences between conventional and organic herds and changes in antimicrobial resistance after conversion to organic farming will be evaluated using in vitro susceptibility data. Use of antibiotics and degree of antimicrobial susceptibility will be treated as continuous variables to show a possible dose-response effect. Multivariable random-effects logistic regression models will be constructed using Proc Genmod in SAS with resistance as dichotomous dependent variable. A similar mixed-effect model will be constructed using Proc Mixed in SAS with MIC as continuous dependent variable.

Dynamics of resistance will be evaluated by looking on changes in antibiotic resistance and in the medication policy. Analysis will be based on the initial analysis of medication from registrations of medicine use and the qualitative research interviews. Methods will be univariate and multivariable methods (factor analysis and correspondence analysis).

Deliverables

3. Determination of the difference in the occurrence of antimicrobial resistance in conventional and organic dairy herds. (Pu)
6. Description of the dynamics of antimicrobial resistance over time. (Pu)
8. Description of changes in disease incidence and antimicrobial resistance after conversion to organic farming. (Pu)

Milestones

- M1 Determination of the difference in the occurrence of antimicrobial resistance in conventional and new and old organic dairy herds.
- M10 Description of the dynamics of antimicrobial resistance over time
- M12 Collection of fecal samples
- M14 Evaluation of changes in antimicrobial resistance from conversion until 3½ years after conversion to organic farming.

WP3: Characterization of treatment pattern in organic dairy herds

Workpackage number:	3	
Start date or starting event:	04-2001	
Responsible person:	MV	
Contributing persons:	MV	TWB
Person-months:	5	1

Objectives

- To characterise the treatment pattern in organic dairy herds
- To analyse the association between treatment frequency and choices and the mastitis pattern in organic dairy herds

Description of work

Implementation of a recording plan in a number of organic herds

In an on-going project, systematic clinical examinations have been introduced in order to describe udder health. These examinations will be introduced in 5 private organic herds. Two kind of systematic clinical examinations are included: systematic clinical monthly examinations of healthy cows and systematic follow-up after mastitis outbreak. Standardised recordings of somatic cell counts on cow and herd level, veterinary treatments, bacteriological findings in mastitis cases, and other herd health and production data will be introduced as well. In this way, data describing the treatment pattern and the choices of the herd manager will be collected based on objective data. In relation to clinical or subclinical infections, the clinical outcome after treatment or no treatment will be registered. This should enable a description of the effect of the more limited treatment frequency in organic farms.

Interviewing herd managers about treatment routines

The background and choice of strategy as experienced by the farmers, as well as the dialogue and decision elaborating process in co-work with other persons (e.g. veterinarian) will be described by means of direct observations and qualitative research methods. Method triangulation and qualitative research interviews will be used and analysed within the framework of grounded theory analyses. This analysis of the choices of the farmer is expected to be necessary when developing guidelines for treatment strategies.

Data analysis and guide lines for treatment strategies

Data analysis will be performed. In-depth analyses will be performed in the 5 herds having undergone very detailed studies (both qualitative interviews and clinical examinations). Data from 40-45 organic herds participating in other project activities will be used in a more large scale epidemiological approach, where somatic cell count patterns will be analysed along with analyses of treatment patterns.

Deliverables

5. Description of the combination of qualitative studies of treatment choices and quantitative data. (Pu)

9. Recommendations for treatment strategies in organic dairy herds (Danish report). (Based on WP3 and WP4)

Milestones

M1 Selection of herds and implementation of clinical examination.

M7 Qualitative analysis on herd level of treatment pattern carried out.

M9 Analysis of data from 5 herds (in-depth studies) and 40-45 herds (overall level; standardised health and production recordings)

M15 Recommendations regarding treatment strategies (Danish report)

WP4: Use of herd specific plans for control of antibiotic resistance

Workpackage number:	4
Start date or starting event:	10-2001
Responsible person:	SMT
Contributing persons:	TWB MV
Person-months:	4 1

Objectives

- To evaluate the use of herd specific plans for controlling antibiotic resistance

Description of work

Formulation and implementation of a plan for reduction of antibiotic resistance.

In collaboration with the local veterinarians a plan for prevention and reduction in occurrence of antibiotic resistance will be prepared in 10 organic herds, including the 5 herds involved in WP2 and WP3.

The plan should consist of the following elements:

- Description of risk areas for antibiotic resistance, partly based on microbiological monitoring.
- Disease prevention plans, including as a minimum mastitis, calf diarrhoea and pneumonia
- Herd specific treatment policy, including monitoring of disease, use of microbiological tests, choice of treatments including use of non-antibiotic treatment and choice of drugs.

The herds will be followed in a 1½ year period following the initial ½ year period of the five herds in WP2 and WP3.

Deliverables

9. Recommendations for treatment strategies in organic dairy herds in (Danish report).
 10. Description of the effect of change in treatment strategies on the occurrence of antimicrobial resistance

Milestones

- M2 Selection of herds and determination of initial occurrence of antimicrobial resistance
 M6 Preparation of herd specific plans
 M8 Midway evaluation and correction of plans
 M11 Final evaluation of plans and status of occurrence of antimicrobial resistance.
 M15 Recommendations (Danish report) including results from WP3
 M17 Analysis of change in antibiotic resistance and changes in use of medicine

7. Implementation and time schedule**Table 3: Deliverables list**

Deliverable No	Deliverable title	Delivery month	Meeting	Nature
1	Data on disease, use of medicine and clinical cases of mastitis	Continuos		O (Data)
2	General meeting 1	11- 00	G1	
3	Determination of the difference in the occurrence of antimicrobial resistance in conventional and organic dairy herds.	09- 01		Pu
4	General meeting 2		G2	
5	Description of the combination of qualitative studies of treatment choices and quantitative data analysis.	06-02		Pu
6	Description of the dynamics of antimicrobial resistance over time.	07-02		Pu
7	General meeting 3	11-02	G3	
8	Description of changes in disease incidence and antimicrobial resistance after conversion to organic farming.	07-03		Pu
9	Recommendations for treatment strategies in organic dairy herds	07-03		Re
10	Description of the effect of change in treatment strategies on the occurrence of antimicrobial resistance	07-03		Pu
11	General meeting 4	08-03	G4	
12	Final status report	08-03		Re

Table 4: Time table

Project month	2000												01												02												03															
	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12							
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40											
WP1																																																				
Monitoring of use of medicine		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x								
M3 Est. of a system for registration of use of drugs and disease in herds										x																																										
M4 Introduction of registration of clinical cases of mastitis													x																																							
M13 Termination of data collection																																																				
WP2																																																				
M5 Det. of the diff. in the occurrence of antimicrobial resistance..													x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x					
M10 Description of the dynamics of antimicrobial resistance over time																					x																															
M12 Collection of fecal samples														x							x				x																											
M14 Evaluation of changes in antimicrobial resistance from conversion...																																																				
WP3																																																				
Characterization of treatment									x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
M1 Selection of herds and implementation of clinical examination.													x	x																																						
M7 Qualitative analysis on herd level of treatment pattern carried out.																							x																													
M9 Analysis of data collected from 5 herds and 40-45 herds																																																				
M15 Recommendations (Danish report)																																																				
WP4																																																				
Use of herd specific plans for control of resistance													x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
M2 Sel. of herds and det. of initial occurrence of antimicrobial resistance													x	x																																						
M6 Preparation of herd specific plans																					x	x																														
M8 Midway evaluation and correction of plans																																																				
M11 Final evaluation of plans and status of occurrence of antimicrobial resistance.																																																				
M16 Recommendations (danish report)																																																				
M17 Analysis of change in antibiotic resistance and changes in use of medicine																																																				
General meetings									x																																											
Status reports										x																																										

8. Collaborative partners

The data on antibiotic susceptibility will be used for comparison with the project “Dairy farming in the post-antibiotic era: The association between antibiotic usage and microbial antibiotic resistance”. This project is co-ordinated by Dr. Paul Bartlett at the Michigan State University (MSU). The project looks at antimicrobial susceptibility and use of medicine in organic and conventional farms in USA. Research professor Stig M. Thamsborg is part of this project with responsibility for the coordination of the comparison of data between USA and Denmark. Torben W. Bennedsgaard will work at MSU for six month in 2000 as part of the US-project.

9. Budget

Institution 1	2000	2001	2002	2003
Salary (scientific)	19	19	19	19
Salary (technical)		100	195	100
Operation		30	60	30
Overhead	3.8	29.8	54.8	29.8
Total	22.8	178.8	328.8	178.8
Institution 2				
Salary (scientific)	28.5	85.5	57	57
Salary (technical)				
Operation		10	20	10
Overhead	5.7	19.1	15.4	13.4
Total	34.2	114.6	92.4	80.4
Institution 3				
Salary (scientific)	28.5	60	163	114
Salary (technical)		53	30	25
Operation	5	40	25	15
Overhead	6.7	30.6	43.5	30.8
Total	40.2	183.6	269.5	190.8
Total	97.2	477.0	682.8	444.0

10. References

Aarestrup FM, Bager F, Madsen M, Jensen NE, Meyling A, Wegener HC. 1998. Surveillance of antimicrobial resistance in bacteria isolated from food animals to antimicrobial growth promoters and related therapeutic agents in Denmark. *APMIS* 106: 606-622.

Aarestrup FM. 1999. Association between the consumption of antimicrobial agents in animal husbandry and the occurrence of resistant bacteria among food animals. *Int. J. Antimicrob. Agents* 12: 279-285.

Hughes VM, Datta N. 1983. Conjugative plasmids in bacteria of the 'pre-antibiotic' era. *Nature* 302: 725-726.

Vaarst, M. 1995. Sundhed og sygdomshåndtering i danske økologiske malkekvægbesætninger [Health and disease control in Danish organic dairy herds]. Ph.D. afhandling forsvaret 24. marts 1995. Pp. 152.

Vartdal, B. & Blekesaune, A. 1992. Sociale sider ved økologisk jordbruk. Ein sociologisk studie av omleggingsprocessen. Senter for bygdeforskning, rapport nr. 1/92, pp. 77.

WHO. 1997. The medical impact of the use of antimicrobials in food animals. Report of a WHO meeting, 13-17 October, Berlin, Germany. World Health Organization, Geneva, Switzerland.

Appendix: CV's of central persons, and description of role, qualifications, capacity and experience of each participant including maximum 5 relevant papers (max. 5 pages).