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Strategies for reduced antibiotic usage in dairy cattle farms

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ABSTRACT

The need for antibiotic treatments in dairy cattle farms can be reduced by a combined intervention scheme based on: (1) timely clinical inspections, (2) the assessment of animal-based welfare parameters, and (3) the use of predictive laboratory tests. These can provide greater insight into environmental adaptation of dairy cows and define animals at risk of contracting disease. In the long-term, an improved disease control justifies the adoption of such a combined strategy. Many antibiotic treatments for chronic disease cases are often not justified with a cost/benefit analysis, because the repeated drug administration does not give rise to the expected outcome in terms of animal health. In particular, compared with untreated cases, antibiotics may not lead to greater cure rates for some forms of mastitis. Lastly, a substantial reduction of antibiotic usage in dairy farms can be achieved through the proper use of immunomodulators, aimed at increasing immunocompetence and disease resistance of cows.

1. Introduction

Production diseases of farm animals are complicated by the overuse of antibiotics, the generation of drug-resistant bacteria, and the transfer of the latter to the food chain. These issues were highlighted in a report issued in 2009 by the European Centre for Disease Prevention and Control and the European Medicines Agency (ECDC/EMEA, 2009), which stressed the discrepancy between the increasing occurrence of multidrug resistant bacteria in Europe and the poor development of antibiotic drugs to treat infections by such bacteria. The animal origin of some serious human infections caused by multidrug-resistant bacteria has also been highlighted by Fey et al. (2000).

The aforementioned risks can be traced to intensive animal production (Ingvartsen et al., 2003), compounded by mismanagement, especially in terms of nutrition, chemotherapy and housing conditions (Trevisi et al., 2006). Indeed, adequate animal welfare is not only achieved by eliminating pain, injury, disease, or distress, but also by proper management (Loor et al., 2013). High production levels and poor management often translate into increased replacement rates, reduction of life expectancy, more frequent occurrence of multifactorial diseases (Mulligan and Doherty, 2008), and increased use of veterinary drugs. The dairy farming sector is no exception to this general rule. A general improvement of milk quality has accompanied an impressive increase of milk yield in Friesian cows. According to the Italian Holstein Friesian Association (ANAFI), in 2011 the average milk yield of 1,128,626 Italian Holstein Friesian cows was 9190 kg with average contents of 3.67% and 3.35% for fat and protein, respectively. The impact of performances like these on animal welfare and health has been considerable. In this respect, as the genetic ability to produce milk increases, more cows are affected by production diseases. The associations between increased milk production and increased risk of production diseases, as well as reduced fertility, are well known, but less is known about the biological mechanisms behind these relationships (Ingvartsen et al., 2003; Oltenacu and Broom, 2010). Thus, the number of cows that reached 48 months of age in the North-Eastern USA decreased from 80% in 1957 to 13% in 2002, and the mean calving interval increased from 13 to 15.5 months (Oltenacu and Broom, 2010). In particular, as reviewed by Bertoni et al. (2009), the high yielding dairy cow (HYDC) is more susceptible to infectious diseases (namely mastitis) and metabolic stress, and this condition is exacerbated in times of reduced immunocompetence as it occurs during the transition from dry period to lactation (Lacetera et al., 2005; Sordillo et al., 2009a; Trevisi et al., 2011a).

In this framework, pending the enactment of a specific directive concerning welfare of dairy cows in Europe, dairy farms are still characterized by the presence of neglected sectors. In terms of housing, hygiene and feeding conditions, heifers and calves are

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often reared under substandard conditions as compared to lactating cows. This stance of farmers arises from lack of awareness of the crucial role of these animals for the maintenance of a good animal health status on farm, and of the repercussions of diseases early in life on the subsequent well-being and milk production levels (Bach, 2011). As a result, calves and heifers are often prone to suffer from opportunistic microbial infections which lead to a high infectious pressure in the herd. This may have a very negative impact on HYDC, that are not likely to mount an effective immune response because of the severe metabolic stress around calving and onset of lactation (Bertoni et al., 2008; Sordillo and Aitken, 2009b; Trevisi et al., 2012). Also, there is evidence of genome changes in HYDC. These may be associated with defective homeostatic control mechanisms, underlying more frequent occurrence of production diseases. Accordingly, some studies demonstrated unfavorable genetic correlations between milk yield and incidence of ketosis, ovarian cysts, mastitis and lameness in dairy cattle (Ingvartsen et al., 2003).

Owing to the above, the purpose of this manuscript is to define measures for a substantial reduction of drug usage in dairy cattle farms on the basis of published studies. The operational framework of these interventions also will be described against the background of the present needs and priorities of farming activities worldwide.

2. Conceptual framework

The achievement of high production levels in animal husbandry translates into a greater difficulty of numerous animals to adapt to the environment. Dairy cows in the post-calving period represent a model of utmost importance and relevance for animal scientists. The current high-genetic merit cow phenotypes demand high technical and management skills, suitable logistical structures and intensive on farm controls. Therefore, an obvious gap may arise between the cow requirements and the actual environment in which they are reared. This fundamental risk condition may co-exist with the high level of performance for a period of time. However, performance will then decrease and eventually cease when clinical diseases and/or serious metabolic dysfunctions occur. Both conditions lead to the same result: early removal of the cows from the production enterprise and an overall increase of replacement rates in the farm. In this respect, the productive increase obtained through genetic selection is not in itself a cause of a reduction in animal welfare. It is a factor causing that a portion of the animal population is unable to respond with an adequate adaptation strategy to the environmental stressors associated with housing, feeding and farm management as a whole.

The disease control strategies in herds affected by production diseases and large antibiotic usage should be supported by adequate risk analysis and management. In this respect, a recent report (EFSA, 2012) provides a useful methodology for prioritization and management of risk factors underlying production diseases. In particular, production diseases are clearly indicated in the section "Consequence characterization flow chart of animal welfare", which outlines an interesting operational framework for intervention strategies. These can be conveniently supported by nation or region-wide information systems of food safety, as recently shown by the development of a risk prioritization model in the Veterinary Prevention Programme (VPP) adopted by the veterinary authorities in the Lombardy Region, Italy.

Secondly, the disease control measures should meet the consumers' expectations and ensure the quality of animal products along with animal health and welfare conditions. At the same time, the adopted measures should be conducive to optimal living conditions in rural areas for farmers and their families, as well as to reasonable prospects of economic sustainability and development of farms. Thus, the adopted measures should lead to lower rates of replacements on farm and improve animal-based welfare parameters. At the same time, livestock capital on farm must remain sufficiently profitable.

Thirdly, in terms of environmental sustainability, nitrogen, carbon dioxide and methane emissions from animal production account for a relevant percentage of the global warming effects (18% in developing Countries and 2–4% in industrialized Countries; Pulina et al., 2011). Moreover, world meat production should double by 2050 to keep up with consumption, thus creating a heavy impact on the biosphere (WWI, 2013). This means that intervention strategies for production diseases must be viewed in the perspective of new, environmentally-friendly husbandry activities.

3. Alternatives to antibiotics

The recent OIE/IABS international conference on "Alternatives to antibiotics" (OIE/IABS, 2012) provided evidence that a reduction of antibiotic usage in farm animals can be achieved by a proper combination of natural antibacterial peptides, biological response modifiers (BRM), pre and probiotics, as well as by a correct development of the gut microbiome. Some of the above approaches have been successfully applied to disease models of cattle. In particular, there is evidence that probiotics can provide an important contribution to disease control in dairy cattle herds (Frola et al., 2012; Nader-Macías et al., 2008). Likewise, several BRM and non-antibiotic drugs proved effective in field trials in terms of disease resistance and thriftiness of treated cattle (Malinowski, 2002). The costs of such treatments are usually comparable to those of vaccines. However, their use implies a proper herd surveillance program, which must define the phases at risk for disease occurrence. In a global view, this means that a satisfactory level of veterinary control is highly-recommended before choosing the above intervention strategies.

On the whole, the authors agree with the conclusions of the OIE/IABS conference and believe that the possible interventions on farm can be widened to further areas of activity:

- The timely detection of disease signs, allowing for shorter and more effective drug treatments.
- A cost/benefit analysis of repeated antibiotic treatments in terms of animal health and farmer's convenience.
- A second generation diagnostic approach to production diseases. This should be based on clinical immunology and chemistry tests predictive of production diseases in dairy cattle, i.e. on robust, user-friendly parameters associated to poor environmental adaptation and relevant high risk of disease occurrence in cattle (Amadori et al., 1997; Trevisi et al., 2012; Loor et al., 2013).

Therefore, on the basis of their own experience and published results, the authors illustrate the possible contributions of the above approaches to an integrated strategy for reduction of antibiotic usage in dairy farms.

4. Early diagnosis and predictive laboratory parameters

High disease rates are commonly reported among HYDC in the transition period, ranging from 3 weeks before to 3 weeks after calving. This period is characterized by the occurrence of an inflammatory response in terms of both positive and negative acute phase proteins (APP+ and APP−, respectively) (Bertoni et al., 2008; Trevisi et al., 2009). To measure the inflammatory response, we developed the Liver Functionality Index (LFI), which is based on some APP- responses (albumin, cholesterol *sensu stricto* + bilirubin) during the first month of lactation (Trevisi et al., 2011a). In this respect, low LFI values are associated with high inflammatory responses and disease occurrence (Trevisi et al., 2012). The relationship between LFI and inflammatory cytokine response was further investigated from day −28 to day +28 with respect to calving in a cohort of 54 high-yielding dairy cows in two experimental dairy farms. During the study, cows were submitted to clinical inspections, blood samplings, as well as to microbiological and milk production checks. The hypothesis being tested was that LFI and APP− on the whole could be used as readout of successful vs. non-successful adaptations to the transition period, with a strong association to disease occurrence. Frequencies of common diseases detected in the transition period in the two herds, with cows ranked in accordance with their LFI values, are reported in Table 1. The cows were divided into 3 LFI groups: low (LOLFI), intermediate (INLFI) and high (HILFI) values, which represent poor, intermediate and good predicted clinical conditions, respectively, in terms of consequences of the inflammatory challenge occurring around calving (Trevisi et al., 2011a, 2012). The prevalence of health problems recorded during the study was evaluated by χ^2 analysis (PROC FREQ of SAS Inst. Inc., Cary, NC, release 9.2) to determine whether prevalence significantly differed among groups of LFI. LFI values, numbers of clinical cases and costs of drug treatments in each group of LFI were analyzed using ANOVA (SAS Inst. Inc.), with group as a fixed factor and herd as a block.

In agreement with our hypothesis, and in both herds, LOLFI cows experienced many more disease cases (Table 1) and related drug treatments (Table 2) until day +28. Thus, the costs of drug treatments were 2 to 4-fold greater in LOLFI compared with HILFI cows. Interestingly, the difference was higher in herd 1 where the monitoring of animals was more precise (e.g. daily measurement of rectal temperature and dry matter intake, frequent assessment of metabolic profile and milk composition). In particular, when animal health data of the two herds were elaborated together, the number of cows without clinical signs in the transition period tended to be lower in HILFI compared with LOLFI animals ($P < 0.08$). Likewise, the number of clinical cases per cow was significantly lower in HILFI compared with LOLFI cows ($P < 0.01$). Moreover, HILFI cows had a lower incidence of retained placenta ($P < 0.05$) and ketosis ($P < 0.07$). As a consequence, the overall costs of drug treatments were significantly higher in LOLFI compared with HILFI cows ($P < 0.01$). The costs of each category of drugs (antibiotics, anti-inflammatory and galenics) were significantly higher in LOLFI versus HILFI cows ($P < 0.05$). Interestingly, the statistical analyses demonstrated a significant effect of either the LFI factor ($P < 0.01$), or the LFI-Herd interaction ($P < 0.05$), which suggests as many areas of intervention in animal care.

Moreover, serum interleukin(IL)-6 concentrations were always greater in LOLFI cows ($P < 0.05$ on day +28 vs HILFI cows), as previously reported by Trevisi et al. (2012). From the dry period onwards the greater serum IL-6 levels were correlated with greater ceruloplasmin (APP+) and lower lysozyme concentrations ($P < 0.05$ and < 0.1, respectively).

These results imply that cows at higher risk for disease occurrence could be identified in the non-lactating period. This way, they could be timely selected for proper healthcare after calving. A possible preventive treatment could be based on anti-inflammatory drugs, which actually promote improved animal health and welfare conditions on farm (Bertoni et al., 2004; Trevisi et al., 2005; Trevisi and Bertoni, 2008). Another promising alternative to antibiotic treatment is immunonutrition (Calder, 2003), i.e. the possible modulation of the immune system by specific nutrients. In this respect, interesting results were obtained by supplementing ω3-fortified feeds (Trevisi et al., 2011b; Grossi et al., 2013), antioxidants (Sordillo and Aitken, 2009b), phytoextracts (e.g. *Echinacea purpurea*, Trevisi et al., 2008) or whole plants around calving (e.g. *Aloe arborescens*, Trevisi et al., 2013). The outcome of these treatments could be evaluated with respect to control groups as significant differences of one or more of the following parameters in the periparturient period: prevalence of disease, milk cell counts, energy metabolism, degree of lipomobilization and related risk of ketosis, drop of Body Condition Score (BCS) and productive performance.

The complex of the above interventions is likely to greatly restrict the number of antibiotic treatments, as well as their duration. Also, in the authors' experience, a strict program of clinical inspections was the foundation of a dramatic reduction of antibiotic treatments. The indicators of animal health and welfare to be monitored during the transition period should include: dry matter intake (or, more convenient, the rumination activity; Soriani et al., 2012), rectal temperature, placenta expulsion, post-calving uterine infections, locomotion score, milk somatic cell count, progression of milk yield, fibrin clots in milk and teat lesions. In particular, early diagnosis and start of relevant pharmacological treatments can greatly improve the effectiveness of drugs and prevent the onset of chronic disease cases. The positive impact of early diagnosis was verified in the trial reported in Table 1, where diagnosis of disease conditions was always performed at a very early stage. As a result, the course of the disease cases was quick; these were often solved by using treatments with galenic remedies, or by stimulating the appetite and the rumination activity (e.g. by means of yeasts and/or glucogenic supplements).

5. Cost/benefit analysis of repeated antibiotic treatments: the mastitis model

Antibiotics are still a very useful tool for veterinary practitioners, and they are not completely dispensable. Whereas proper

Table 1
Disease cases in periparturient cows with different levels of acute phase response.

Herd	LFI group	Cows	LFI		RP	MET	KET	MAST	LAM	Fever	Other	Overall health problems	Disease cases per cow	Cows without clinical signs
		n.	*Average*	*St. dev.*	*n.*	*n.*	*n.*	*n.*	*n.*	*n.*	*n.*	*n.*	*n./cow*	*n.*
1	LOLFI	7	−3.02[a]	1.50	3	1	1	3	0	2	3	13	1.86[c]	2
	INLFI	6	−0.54[b]	0.52	1	0	1	2	0	1	1	6	1.00[ab]	1
	HILFI	7	1.27[c]	0.57	0	0	0	1	0	1	0	2	0.29[a]	5
2	LOLFI	11	−3.76[a]	1.37	1	2	2	1	0	6	9	21	1.91[c]	2
	INLFI	12	−1.13[b]	0.80	0	4	1	1	1	4	2	13	1.08[ab]	5
	HILFI	11	1.94[c]	1.24	0	2	0	1	1	2	2	8	0.73[a]	4
Overall		54	−0.91	2.39	5	9	5	9	2	16	17	63	1.17	19

Disease frequency in the first month of lactation in multiparous dairy cows, belonging to two herds ranked in tertiles of Liver Functionality Index (LFI): low (LOLFI), intermediate (INLFI), high (HILFI) LFI. Data were collected in an experimental farm as an extension of a previous published study (Trevisi et al., 2012).
Different superscripts indicate significant differences within the herd ($P < 0.05$).
LFI, liver functionality index; RP, retained placenta; MET, metritis; KET, ketosis; MAST, mastitis; LAM, lameness; Fever, rectal temperature >39.5 °C (also without additional clinical signs); Other, other disease cases.

Table 2
Costs of drug treatments in periparturient dairy cows.

Herd	LFI group	Cows	Antibiotics (1)		Other drugs (2)	Galenic (3)	Overall
			Treatments		Cost		
		n.	*n./cows*		*€/cow*		
1	LOLFI	7	1.71[b]	53.9[b]	47.06[b]	15.65[b]	116.6[b]
	INLFI	6	0.50[a]	8.6[a]	10.45[a]	10.63[ab]	29.7[a]
	HILFI	7	0.29[a]	8.5[a]	17.37[a]	1.22[a]	27.1[a]
2	LOLFI	11	0.73	11.9	17.6	23.7	53.2
	INLFI	12	0.58	13.6	12.0	20.6	46.1
	HILFI	11	0.36	10.0	5.1	14.2	29.3
Overall		54	0.66	16.5	16.8	15.7	49.0

Average costs (*€/cow*) for drug treatments in the first month of lactation in multiparous dairy cows, ranked in tertiles of Liver Functionality Index (LFI): low (LOLFI), intermediate (INLFI), high (HILFI) LFI. Data were collected in an experimental farm as an extension of a previous published study (Trevisi et al., 2012). Different superscripts indicate significant differences within the herd ($P < 0.05$). These were not observed in herd 2 because of a greater individual variability.
Notes: (1) includes antibiotics for intramuscolar, intravenous, intramammary and intrauterine administration; (2) includes anti-inflammatories and other drugs which demand to discard milk after their use; (3) vitamins and minerals administered orally, i.m. or i.v. (without withdrawal time).

prophylactic treatments are conducive to lesser antibiotic usage, clear and comprehensive therapeutical alternatives are still to be developed. Yet, even in a therapeutical context, a great reduction of antibiotic treatments can be achieved by a critical evaluation of their appropriateness in persisting disease cases. In general, in the bovine mastitis model, there is strong circumstantial evidence that therapy does not always imply healing of infected animals. Healing of cows may not imply a financial advantage for farmers. Under these conditions, therapy of subclinical mastitis mainly aims at obtaining productive efficiency at a reasonable cost.

Is this always the case? The study by Daprà et al. (2006) demonstrated that the mean costs of antibiotic treatments for sub-clinical mastitis varies widely among farms, which means that a farm factor exerts a potent influence on the effectiveness of treatments. Indeed, a recent study involving 125 Italian dairy herds (Zecconi and Bella, 2013; Zecconi, 2013) observed that costs of clinical mastitis varied from 140 to 260 €/case. These differences were mainly due to therapies, because the herd size, animal breed and management were very similar among herds. Moreover, data showed that costs per clinical case of mastitis increased linearly along with the frequency of mastitis (from 200 €/case, when prevalence was <2%/month, to 500 €/case for prevalence >6%/month) (Zecconi, 2013; Zecconi and Bella, 2013). The difference in costs was mainly due to the therapeutic protocols applied. These data indicate that efficient dairy herds have less mastitis. They also achieve optimal mastitis control spending 50% less per case than herds with higher mastitis incidence.

Secondly, the cost-benefit profiles of repeated antibiotic treatments for bovine mastitis turn negative at curing rates of 50% and even 100% if they are performed 3 and 8 times, respectively (Swinkels et al., 2005). Thirdly, a large field study by Wilson et al. (1999) demonstrated that several antibiotic treatments for *S. agalactiae*, *S. aureus*, environmental *streptococci* and coagulase-negative *staphylococci* do not lead to higher curing rates compared to untreated cases. Further, repeated antibiotic treatments for mastitis should be offset against the increased probability of relapses of cows with >3 parities (Pinzon-Sanchez and Ruegg, 2011).

6. The role of immunomodulators

The impact of acute, transient stress is usually adaptive on the immune system; vice versa, chronic stress often implies immunosuppression following the animals' failure to cope (Amadori et al., 2009). As a result, a reduced immunocompetence for environmental pathogens paves the way to a plethora of opportunistic diseases. Under these conditions, the use of BRM (immunomodulators) can be conducive to improved animal health and thriftiness in dairy farms. Thus, it has been demonstrated that an interferon-inducing BRM (UV-inactivated *Parapoxvirus ovis*) can significantly restrict the occurrence of new intramammary infections and the related use of veterinary drugs (Zecconi et al., 1999). The same result can be obtained by a parenteral low-dose treatment with interleukin (IL)-2 (Zecconi et al., 2009). The treatment consisted of a single, 800-picogram IL-2 dose injected subcutaneously into the skin region drained by the supramammary lymph node 3–5 days after calving. The study included 45 cows (23 treated and 22 controls) of three commercial dairy herds. The results showed that the treatment had no side effects and caused a significantly higher frequency of healthy udder quarters until day 17–19 after calving in the treated group, compared to the control one. Although these results should be confirmed by large-scale field studies, they provide important evidence as to how a targeted and site-specific modulation of the local immune response could be an efficient strategy for mastitis control in dairy cattle, leading to a lesser requirement for antibiotics in dairy farms. It goes without saying that each proposed BRM should be thoroughly and carefully tested in dairy cattle beyond the results accumulated in other target species.

7. Conclusions

Based on a correct analysis of the herd's anamnestic data of opportunistic diseases and of farm-specific risk factors, a substantial reduction of antibiotic usage in dairy farms can be achieved by a proper combination of the aforementioned intervention strategies. In this respect, the proper combination of clinical inspections, animal-based welfare parameters and 2nd generation, predictive laboratory tests can provide a greater insight into environmental adaptation of dairy cows and define the animals at risk. The greater potential for disease control in the herd can justify the adoption of such a strategy on a sound cost/benefit basis. Most important, such an intervention can be conducive to a new, crucial role of the veterinary and nutritionist professions, in line with fundamental expectations of legislators, farmers, stakeholders and consumers about food safety.

General and nutritional management of dairy farms has to be primarily committed to prevent animal diseases and to preserve animal welfare; in turn, these activities should be monitored and supported by the National Veterinary Services. The large-scale adoption of the above disease control measures will be conducive to the establishment of minimum requirements in terms of clinical inspection, environmental checks, biosecurity, farm hygiene, feed safety policy and laboratory investigations in dairy farms, with possible favorable repercussions on production costs and animal welfare. These minimum requirements could be recognized in terms of Good Farming Practices (CEC, 2003) and welfare-friendly primary production (CEC, 2012) entitling farmers to higher selling prices and channeling dairy products to properly tagged sale chains. Thus, the definition of economic and environmental sustainability of the proposed control measures will set the basis for an involvement of farmers, veterinary practitioners, dairy extension specialists and veterinary authorities towards better qualification of the food chains and consumers' awareness.

Conflict of interest

None of the authors has financial or personal relationships with any third party, organization or agency that could exert undue influence on the contents of this study and/or lead to any deliberate bias.

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