Immunoprophylaxis in intensive farming systems: the way forward

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A B S T R A C T

High levels of production in intensive farming systems are associated with increased replacement rates as a result of multifactorial diseases. The so-called “production diseases” may include low-grade infection reducing profitability without increased morbidity. Such infections are sustained by low pathogenic viral and bacterial agents which give rise to full-blown disease in association with poor environmental conditions. In these farms, the results of vaccination may be disappointing. Therefore, fundamental issues should be dealt with toward successful immunoprophylaxis. High lean meat and milk production are associated with chronic inflammation and activation of the innate immune system vis-à-vis cellular stress. This may negatively affect adaptive immune responses. A negative modulation of the host microbiome by farm management practices and drug treatments is a further risk factor. The immune response to stressed cells questions the usual correlates of protection investigated after vaccination. In particular, there is evidence that specific and non-specific immune responses may overlap in vitro as a result of a high level of innate immune responses to Damage-Associated Molecular Patterns (DAMPs) and stress antigens. A vigorous adaptive immune response to microbial agents may be sometimes counterproductive, as suggested in porcine reproductive and respiratory syndrome virus (PRRSV) infection. Alternative outcomes should be sometimes pursued: a better homeostatic control of the inflammatory response, effective and self-limiting innate immune responses, and even tolerance induction. On the whole, successful immunoprophylaxis in intensive farming systems demands co-ordinated and multi-disciplinary efforts in terms of animal breeding, farm management and hygiene, correct choice and harmonization of the prophylactic tools (vaccines, immunomodulators, pre- and probiotics). Finally, there is evidence that disease-predicting parameters of the innate immune response may greatly ease the identification of herds and animals at risk, and contribute to reduced antibiotic usage on farm.

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1. Introduction

The achievement of high production levels in animal husbandry determines a greater difficulty of numerous subjects to adapt to the environment. This translates into increased replacement rates, reduction of life expectancy, more frequent occurrence of variegated and multifactorial diseases and increased use of veterinary drugs. The two most studied models are pigs in the weaning and back grounding phases and dairy cows in the post-calving period. In these phases, an increased incidence of health problems is mostly related to distinct conditional diseases, which cause a significant part of the economic losses related to morbidity, mortality and early removal from the herd. The occurrence of conditional diseases is actually eased by the presence of high-yielding animal phenotypes demanding high technical and management skills, suitable logistical structures and intensive controls by the breeder. Therefore, an obvious gap may arise between the animals’ requirements and the actual environment in which they are reared. This fundamental risk conditions may co-exist for a period of time with high levels of production performance, which will then decrease and eventually cease when clinically overt diseases and/or serious metabolic dysfunctions occur; both cases lead to the same result: early removal of the animals from the production process and overall increase of the farm replacement rates.

In this respect, the productive increase obtained through genetic selection is not in itself a cause of a reduction in animal welfare, but a factor causing a part of the animal population not to be able to respond with adequate environmental adaptation strategies. Genetic selection has worked well to achieve the required increase of production, but not to ensure the full efficiency of the homeostatic mechanisms for adapting to the environment, with obvious repercussions on animal welfare and health. The reduced adrenal response of the present pig phenotypes is a clear example of this tenet (Mormede et al., 2011).

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Owing to the above, the capacity of the present farmed animal phenotypes to mount effective immune responses to vaccines and microbial pathogens should be questioned and proper study models should be developed. In addition to that, the background of stress response in these animals is likely to influence the usual correlates of immune protection and give rise to confounding pictures. Lastly, the type of adaptive immune response to be pursued should be also questioned in view of conflicting data sets regarding immune response and disease sustained by common microbial pathogens. These three issues are dealt with in this review paper, aimed at indicating major hurdles and inconsistencies, as well as possible ways forward.

2. Risk of disease occurrence

The need for efficient logistics and infrastructure, and proper stockman’s assistance in intensive farms can be adequately grasped on the basis of the astounding productive performances of farm animals. As for swine, daily weight gains of 800–900 g in the finishing phase, 13–14 liveborn/litter, 25–28 piglets/sow/year are common performances for the top sow producers (Anonymous, 2009). As for chickens, the production cycle of broilers has been progressively shortened to some 35 days to obtain subjects of 2 kg live weight and a final conversion index around 2.0 (see e.g., the AVIAGEN technical reports on ROSS broilers). In this framework, production diseases of farm animals have been recognized as multi-factor affections associated with the present conditions of intensive husbandry and the animal phenotypes employed to this purpose.

Owing to the above, certain animal phenotypes that show high production levels are at a higher risk for disease occurrence, as shown e.g., by the correlation, in the Eighties, between appearance of PRRS in swine and lean type hybrids, which turned a subclinical viral infection into a serious animal health problem (Amadori and Razzuoli, 2014). In a global perspective, the increased use of veterinary drugs associated with production diseases constitutes a major threat to the overall food safety levels. In this respect, the critical correlation between animal welfare, animal health and food safety can be defined by the chain of events depicted in Table 1. These imply that chronic stress models are much more relevant to the above concepts than acute stress models, since the effects of stress on the immune system are generally adaptive in the short term and harmful over the medium and long ones (Amadori et al., 2009).

Thus, a transient acute stress may be even associated to a better immune response and thought of as nature’s adjutant under field conditions (Dhabhar and Viswanathan, 2005). In practice, over-stimulation of the physiological mechanisms of homeostasis favors the occurrence of a state of immunosuppression, which in turn predisposes to disease onset. The available disease figures in farm animals confirm this fundamental tenet.

Poultry show a frequently high prevalence of outright production diseases. A few years ago, ascites was thought to account for 25% of the overall mortality in broilers, usually estimated between 2 and 4% (Guo et al., 2007). Unofficial estimates of costs due to dysbacteriosis are between 5 and 10 Eurocent per broiler. More importantly, however, dysbacteriosis is estimated to account for between 50 and 70% of antibiotic usage in broilers in the EU. Losses due to necrotic enteritis were estimated many years ago (Van Der Sluys, 2000). An interesting report on the total use of antibiotics associated to production diseases in poultry was recently issued in Belgium (Persoons et al., 2012).

In dairy cattle, a dramatic improvement of milk quality in terms of somatic cell counts went along with an impressive increase of milk yield in Frisian cows. According to the technical report of the Italian Farmers’ Association (AIA), the average milk yield in 651,489 lactations of Frisian cows amounted in 2010 to 9,075 kg, with average contents of 3.64% and 3.31% for fat and protein, respectively. The impact of these performances on animal welfare and health has been considerable. In this respect, as the genetic ability to produce milk increases, more cows have production diseases; the associations between increased milk production and increased risk of production diseases, as well as reduced fertility, are well documented, but less is known about the biological mechanisms behind these relationships (Oltencu and Broom, 2010). Thus, cows alive in North-Eastern USA at 48 months of age passed from 80% in 1957 to 13% in 2002; in the same farms and in the same period the mean calving interval passed from 13 to 15.5 months (Oltencu and Broom, 2010).

According to the official data of the Italian State Statistical Agency (ISTAT), 18 million pigs/year are produced in Italy; 10% (1.8 million) die in the suckling period; 0.72 million die in the first 80 days of life (4%); 0.54 million die in the fattening period (3%); this determines the appalling figure of 17% mortality, which should be evaluated along with 11% (2 million) of young pigs slaughtered in side circuits as a result of diseases preventing the completion of the production cycle. While the above data may be biased by the local peculiarities of the Italian pork production ("heavy" pigs of 160–170 kg at slaughter) and the unknown prevalence of accidental losses (e.g., suffocation of piglets under the sow, electric shock, acute intoxication, road accidents), one may conclude that

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**Table 1**

Consequence characterization flowchart of disease occurrence in intensive farming systems.

<table>
<thead>
<tr>
<th>Chronic stress</th>
<th>Immunosuppression</th>
<th>Conditional diseases</th>
<th>Increased need for antibiotics</th>
<th>Food safety problems</th>
</tr>
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**Fig. 1.** An example of lean type, rapid growth pig phenotype.
production diseases can impact on one third approximately of the pig population in terms of mortality, morbidity and generation of “poor doers” among weaners and growers.

3. Animal phenotypes and immunosuppression: the pig model

The reasons underlying the above disease figures in farmed pigs can be traced back to fundamental features of the present lean type phenotypes (Fig. 1). In particular, the percentage weight of the heart muscle has decreased from 0.38% in wild boars to 0.21% in modern Landrace pigs (Brambilla et al., 2002). Such pigs show an accentuated mean capillary-to-fiber distance in larger (type II) muscle fibres, which hampers an effective removal of toxic metabolites and favors lactic acid accumulation (Dämmrich, 1987). In addition, the resulting tissue hypoxia induces conditions of persistent oxidative stress response, which paves the way to serious clinical conditions like Mulberry Heart Disease (Korpela, 1990). Lean muscle pigs show in fact abnormally high serum concentrations of reactive oxygen metabolites (ROMs), as opposed to rural swine (Brambilla et al., 2002). In the authors’ experience, ROMs levels equivalent to >20mM H₂O₂ can be easily found in lean type pigs. This implies an oxidative stress under resting conditions similar to that of human beings during intense physical exercise (Fig. 2). The apparent paradox of a high release of Reactive Oxygen Species (ROS) in the presence of hypoxia was solved some years ago, when it was discovered that the mitochondrial electron transport chain is actually an oxygen sensor, which reacts to a reduced partial oxygen pressure by releasing ROS (Guzy and Schumacker, 2006). ROS alter proline hydroxylase (PHD), i.e., a fundamental component for ubiquitination and final degradation of the Hypoxia Inducible Factor-α (HIF-α). Under these conditions (Fig. 3), HIF-α can form a functional heterodimer with the constitutively expressed HIF-β, penetrate into the nucleus and give rise to the well-known hypoxia response (Guzy and Schumacker, 2006). This is a crucial feature. There is strong evidence in fact that the hypoxia response is highly detrimental to T cell homeostasis. In particular, hypoxia can affect T cells by blocking proliferation and inducing cell death, while promoting angiogenesis and survival of surrounding cells (Melillo, 2010). The impact on T cells determines inhibition of T cell functions, Th1 to Th2 shift, reduced Tcr-mediated activation (Skitkovsky and Lukashev, 2005). This process is also fueled by ongoing IL-17 responses (Hot and Miossec, 2011). On the whole, hypoxia and HIF-α-driven responses give rise to an altered homeostasis of T cell responses, whereby Th2 and Th17 responses are favored to the detriment of the Th1 and Treg ones (Fig. 4). Also, the above process can be increased by growth factors and cytokines inducing HIF-α protein synthesis through pathways involving PI3K/AKT/mTOR and MAPK (Melillo, 2010). ROS sensors can induce a compensatory response based on the activation of the ARE transcription factor and production of anti-oxidant components like SOD and Gpx (Ramprasath and Selvam, 2013). Nevertheless, there is often a failure of the total anti-oxidant (OXY) response in pigs, as evidenced in disease cases on farm (Brambilla et al., 2002). The above findings should be evaluated in the light of the very high productive performances of lean type pigs. Therefore, if genetic selection is used for high productivity purposes and relevant nutrient profiles are adopted, an outright “metabolic stress” can concur with the endogenous oxidative stress to disease occurrence. The proven correlation between administration of growth hormone in cows and occurrence of mastitis (Anonymous, 1999) clearly outlines the association between metabolic stress and disease occurrence (http://ec.europa.eu/food/fs/sc/scah/out21_en.pdf).

Owing to the above, lean type pigs under conditions of chronic oxidative stress are not likely to mount balanced and effective T cell responses because of a defective homeostasis of the T cell compartment. In the authors’ opinion, this is one of the major structural features affecting the efficacy of adaptive immune responses in pigs. Therefore, correlation studies should be performed between constitutive oxidative stress in pigs and adaptive immune response to vaccines and infectious microbial agents. On the basis of such studies, a case could be made for proper breeding strategies (animal phenotypes less prone to oxidative stress), and for anti-oxidant feeding regimes to support current vaccination protocols and other disease control measures on farm.

In addition to that, conditions of chronic oxidative stress are likely to cause poor homeostatic control of the inflammatory responses. In particular, oxidative stress results in the release of enzymes, named “redoxkines”, that amplify signals of the TNF-α–induced inflammatory response and have also other cytokine-like activities, linking oxidative stress to innate immunity (Salzano et al., 2014).

4. Immune response to stress antigens and correlates of protection

The above data imply the existence of high levels of innate immune response to damage-associated molecular patterns (DAMPs) like uric acid, ATP, oxidative stress products, etc., released by stressed cells. Interestingly, oxidative stress may be the common final pathway of the inflammamome reaction, unifying a plethora of stress-related events (Martinon et al., 2009). Also, neo-antigens expressed on stressed cells like MIC, HSP 60, T10, T22, CD1c, described in mice, humans and also cattle, are recognized by the “Lymphoid Stress Surveillance System” (Hayday, 2009). This high level of baseline immune response often co-exists with further inflammatory stimuli as a result of poor farm hygiene and associated infectious pressure of common environmental pathogens. In pig farms, such an outcome is actually eased by common management practices like:

- Cross-fostering, (a) of piglets beyond 2 days of life, (b) of a high number of piglets/sow, (c) among different pens.
- Co-existence of backward and forward flow of animals among the different production units.
- Lack of all-in-all-out procedures in the farrowing and weaning units.
- Lack of disposable clothing and footwear for personnel on passing to other pens. Lack of adequate quarantine regimes for replacement pigs.

The above features (to name a few) do increase the infectious pressure in pig farms, as shown by the high levels of IFN-γ in many plasma samples of apparently healthy and thriving pigs in the post-weaning and back grounding phases (Amadori M., unpublished results). In this scenario, the Type I IFN response of pigs at 5–6 days after weaning (Razzuoli et al., 2011) represents an important indication of a homeostatic control action vis-à-vis the harmful effects of the early weaning stress (Amadori et al., 2012). Interestingly, infectious pressure should be meant as exposure to both microbial agents and airborne LPS, which is definitely an occupational hazard for pig farm personnel (Zhiping et al., 1996). It goes without saying that such levels of background response to infectious and non-infectious stressors may jeopardize the correct evaluation of recognized immune correlates of protection. Most important, non-specific cross-reactions are likely to be seen in vitro because of the constitutive expression of stress antigens (MIC, ULPB 1–3) in many established cell lines of epithelial and endothelial origin used for propagation and in vitro testing of animal viruses (Tran et al., 2008). In our experience, established cell lines of pig
Fig. 2. Lean type pigs show levels of oxidative stress under resting conditions similar to those of humans during intense physical exercise.

Fig. 3. The mitochondrial electron transport chain is actually an oxygen sensor, which reacts to a reduced partial oxygen pressure by releasing ROS. ROS alter proline hydroxylase (PHD), i.e., a fundamental component for ubiquitination and final degradation of the Hypoxia Inducible Factor-α (HIF-α). Under these conditions, HIF-α can form a functional heterodimer with the constitutively expressed HIF-β, penetrate into the nucleus and give rise to the hypoxia response. Reproduced with permission (Guzy, R.D.; Schumacker, P.T., 2006. Oxygen sensing by mitochondria at complex III: the paradox of increased reactive oxygen species during hypoxia. Exp. Physiol. 91 (5), 807–819. Wiley publisher). © 2006 The Authors. Journal compilation. © 2006 The Physiological Society.

Fig. 4. Under hypoxia conditions a major dysregulation of T cell responses takes place: Th2 and TH17 responses are favored, whereas Th1 and Treg responses are inhibited. The same conditions may be reproduced by other inflammatory stimuli activating the HIF signaling pathway.

(PK-15c28) and monkey (MARC-145) do express such stress antigens on their surface, as established by means of a NKG2D-human Fc chimera (Zanotti et al., 2015). This may have serious repercussions on immunoassays for viruses like PCV2 and PRRSV. Thus,
PBMC of PCV2 vaccinated/infected pigs may show a higher response to a control cell cryolyase compared with the relevant virus grown in the same cells in an ELISPOT assay for IFN-γ — secreting cells (Fig. 5). Likewise, the presence of necrotic cell antigens in any assay for inflammatory cytokine responses to microbial agents is likely to raise non-specific responses to high levels. Therefore, whenever purified viruses or viral proteins cannot be used in vitro, proper controls should include the potential DAMPS and stress antigens contained in the raw viral antigen.

**5. Which kind of protective immune response?**

There is a wide consensus in the scientific community that strong and long-lasting adaptive immune responses to microbial agents are generally beneficial to the naïve, uninfected host, with some minor exceptions like Respiratory Syncytial Virus (RSV) infections in cattle (Antonis et al., 2003). The picture is not as clear in animals experiencing an ongoing microbial infection. Thus, there are at least three microbial infections which question the beneficial role of vigorous adaptive immune responses to microbial agents in infected animals:

- **PRRS.** As illustrated in a previous review paper (Amadori and Razzuoli, 2014), PRRS vaccines and high-titered neutralizing antibody can be protective in the naïve host. On the contrary, there is strong evidence that high levels of inflammatory and adaptive immune responses to ongoing infections sustained by some Type I, subtype III, EU PRRSV strains give rise to serious clinical forms of disease and lung pathology. This is not seen in control, uninfected animals and pigs infected with most Type I, subtype I, EU PRRSV strains, giving rise to little if any inflammatory and adaptive immune response. The same outcome can be observed in pigs given particular PRRSV DNA vaccines and later submitted to challenge infection (Amadori and Razzuoli, 2014). These findings are actually reminiscent of the murine Arterivirus model in which viremia levels and time-course are the same in immunologically tolerant and control mice (Rowland et al., 1994), implying a negligible role of adaptive immunity in the clearance of an established Arterivirus infection. These findings should prompt the scientific community to further research efforts in the field of “educated” innate immune responses (Horowitz et al., 2011), as new, enticing scenario for the control of microbial infections.

- **Salmonella.** In the enteric Salmonella infection model, there is strong evidence that a pro-inflammatory immune response of the host changes gut microbiota composition. As a result, Salmonella enterica serovar Typhimurium (Salmonella typhimurium) can overcome colonization resistance exerted by commensal bacteria and give rise to increased infection of gut epithelial cells. Therefore, the host’s immune defence can shift the balance between pathogen and microbiota in favor of the pathogen (Stecher et al., 2007).

- **Fungal infections.** In the Candida albicans model, Th1 and Th17 responses along with the IL23-IL22-defensins loop are badly needed for the control of acute infections. However, in a subsequent phase, dendritic cells (DCs) and T regulatory (Treg) cells dampen the previous levels of adaptive immune response and give rise to “Protective Tolerance”, meant as the host’s immune defense without elimination of the pathogen (Santamaria et al., 2011). It can be argued that such a profile of immune response is beneficial to the host in terms of maintenance of memory and lack of tissue damage (Romani and Puccetti, 2006). The pursuit of “Protective Tolerance” could be also relevant to microbial infections of farm animals, whereby disease signs can be the expression of poorly regulated inflammatory responses in the framework of a high environmental infectious pressure as a result of poor farm hygiene.

**6. The crucial role of microbiota**

The term “host’s microbiota” is meant as the ensemble of microorganisms that resides in an established environment such as gut, skin, mouth, vagina, and so on. Gut microbiota corresponds to the huge microbial population living in the intestine, containing trillions of microorganisms with some 1000 different species, most of them specific to each subject. Beyond recognized nutritional advantages (energy storage, B and K vitamin production, short-chain fatty acid production), the main properties of microbiota associated with disease resistance include inhibition of pathogens colonization, degradation of xenobiotics and stimulation of both development and maintenance of the immune system (Del Chierico et al., 2012). Microbiota can prevent pathogens colonization by increasing the speed of intestinal transit, competing for space and nutrients and exerting an outright amensalism, i.e., the production of substances (like lactic and short-chain fatty acids, hydrogen peroxide, orbacteriocins) toxic for other microbial species. These...
properties underlie the efficacy of “Competitive Exclusion” procedures (Kerr et al., 2013), as well as of lattobacilli and other probiotics in the prophylaxis of farm animal diseases (Nader-Macias et al., 2008; Espeche et al., 2012). Accordingly, a probiotic mixture that contains Lactobacillus rhamnosus and Lactobacillus helveticus was shown to prevent C. rodentium-induced mortality in neonatal mice, whereas treatment of mice with streptomycin prior to C. rodentium infection resulted in a 10–50-fold increase in the abundance of C. rodentium in the gut (Collins et al., 2014). There is also evidence that probiotics can act as powerful adjuvants for mucosal Rotavirus vaccines in the gut, as well as modulators of a better response of the host to Rotavirus infection (Vlasova et al., 2016).

Most important, the correct development and maintenance of innate and adaptive immune defense mechanisms in the mucosal and peripheral districts are highly dependent on the gut microbiota (Macpherson and Harris, 2004). In turn, immune cells provide effector functions that maintain a stable microbiota, in the framework of mechanisms aimed at mutual homeostasis (Thaiss et al., 2014). Also, the gut microbiota exerts a substantial inflammatory control of the gut ecosystem. Commensal bacteria can inhibit NFKB activation by disrupting the host cell control over ubiquitination and degradation (Neish et al., 2000), and they can also stimulate IL-10 responses by releasing metabolites of complex digested polysaccharides (Saemann et al., 2000).

The issue of microbiota is of paramount importance for the immune control of microbial infections since established farm management practices in poultry and pig farms do affect the normal development of gut microbiota.

As for poultry, the separation between hatching and farm sites implies defective colonization of microbiota. Disease resistance would not adequately develop, since adult fowl microbiota could not exert a positive imprinting in the first days of life (Stanley et al., 2013). This risk condition may be related to the development of intestinal dysbacteriosi (Teirlync et al., 2011), which is in turn associated with increased pathogen colonization in the gut (Ducatelle et al., 2015).

In pigs, early weaning at 3–4 weeks of age implies a risk for animal health (Amadori et al., 2012). This is the reason why antibiotic treatments are frequently carried out in this phase. These undoubtedly cause short and long-term repercussion on animal health, based on a substantial reduction of intestinal bacterial community diversity (Janczyk et al., 2007). Also, the tendency to antibiotic-resistant bacterial strains is increased by co-treatments with zinc oxide and antibiotics at weaning (Bednorz et al., 2013). Most important, antibiotic treatments in piglets could have later unfavorable repercussions in terms of animal health. Although scanty data are available in the pig model, there is instead strong evidence in humans that disruption of the microbiota with oral antibiotics often precedes the emergence of several enteric pathogens (Pavia et al., 1990; Pepin et al., 2005). These exploit the disruption of microbiota by catabolizing microbiota-liberated mucosal carbohydrates during their expansion within the gut (Ng et al., 2013). Also, these data are in agreement with the streptomycin-treated mouse colitis model, which mimics human disease after elimination of gut microflora (Ilg et al., 2009). There is no reason why this tenet should not hold true in the pig intestine, too. In particular, the pro-inflammatory effects of antibiotic treatments in the gut due to microbiota disruption might be of some importance. Interestingly, a field study on pigs submitted to antibiotic treatments at weaning demonstrated significantly higher plasma LPS concentrations in “problem” herds, compared with “healthy” controls (0.21 ± 0.1 vs. 0.08 ± 0.06 ng/ml, P < 0.005), accompanied by significantly higher levels of IFN-γ and IL-12 (P < 0.02) (Candotti, Rota Nodari and Amadori, unpublished results). Accordingly, as stressed in a review paper of ours (Amadori et al., 2012), intestinal permeability at weaning is the likely result of an IFN-γ response (Beaurepaire et al., 2009) in the framework of a major inflammatory response to the early weaning stress (Pie et al., 2004). The aforementioned microbiota disruption would exacerbate such a process and cause a reduced competitive exclusion of pathogenic bacteria. Further studies are needed to define the possible long-term influence of antibiotic treatments on later outbreaks of disease sustained in pigs by Lawsonia intracellularis (Porcine proliferative enteritis) and Brachyspira hyodysenteriae (Swine dysentery).

7. Vaccination and immunomodulation

The concepts illustrated in the previous sections outline widely different properties of the microbial agents associated with farm animal diseases and diverse possible host/pathogen relationships. This demands flexible disease control strategies aimed at a cost-effective prevention of losses and antibiotic usage on farm. The latter issue is nowadays of major importance because of the recognized role of drug treatments in farm animals in the generation of multi-drug resistant pathogenic bacterial strains (Fey et al., 2000), and because of the poor development of new effective antibiotic molecules to face such a fundamental threat. This was clearly indicated by the European Centre for Disease Prevention and Control and the European Medicines Agency (ECDC/EMEA, http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf). Owing to the above, successful immunophylaxis in intensive farming systems demands co-ordinated and multi-disciplinary efforts in terms of animal breeding, farm management and hygiene, correct choice and harmonization of different prophylactic tools (vaccines, immunomodulators, pre- and probiotics). The latter should be adopted on the basis of a correct analysis of the animal health status on farm, to be offset against farm logistics and infrastructure and availability of resources. On a genuine immunological basis, disease outbreaks caused by widespread, opportunistic microbial agents should be generally targeted by proper immunostimulation treatments with Biological Response Modifiers (BRM) or synthetic products. These have proved effective in field trials under controlled experimental conditions for a long time (Mayr et al., 1986). Such products should be used in healthy animals just before the critical phase in which increased disease prevalence is observed (e.g., weaning, transportation, commingling of groups). The treatments are meant for an increased disease resistance as a result of adequate immunocompetence of farm animals vis-à-vis common environmental pathogens. When the disease problems are due to a dysregulated inflammatory response, disease control can be often achieved by oral, low-dose, interferon–alpha treatments (Cummins et al., 2005). These proved effective in several human and animal models of viral and immunopathological diseases (Tompkins, 1999; Dec and Puchalski, 2008) without the toxic side effects of high-dose parenteral treatments, also seen in cattle (Straub, 1995). In our experience, oral, low-dose interferon–alpha treatments proved effective in outbreaks of respiratory PRRS (Amadori and Razzuoli, 2014), i.e., a disease based on a crucial synergism between PRRS virus and bacterial LPS (van Gucht et al., 2003).

8. Disease risk assessment

The detection of an early innate immune response of farm animals to common non-infectious stressors can be conducive to disease risk assessment, whereas monitoring the same or similar parameters after disease occurrence can be the foundation of effective prognostic systems. In practice, the detection of such responses in critical phases of the farming cycles may represent important evidence of a negative imprinting of the innate immune system after
exposure to environmental and metabolic stressors, which is associated with increased disease prevalence and drug usage in later phases (Trevisi et al., 2012).

The experience accumulated so far in cattle (Bertoni et al., 2008; Trevisi et al., 2012) and in pigs (Moscati et al., 2011) can be the foundation of a second generation diagnostic approach to production diseases of farm animals, based on selected clinic immunology assays. These will deal with robust, user-friendly parameters of innate immunity associated with poor environmental adaptation and relevant high risk of disease occurrence. The greater potential for disease control in the heifers and reduced antibiotic usage (Trevisi et al., 2014) can justify the adoption of such a strategy on a sound cost/benefit basis. Most important, such an intervention is in line with fundamental expectations of legislators, stakeholders and consumers about food safety.

9. Conclusion

The current immunological approaches to disease control in farm animals need a fundamental re-appraisal following the evolution of the farming systems, the globalization of markets, climate changes and, most important, the emergence of disease-susceptible animal phenotypes. The infections sustained by widespread opportunistic microbial agents are not likely to be effectively counteracted by conventional or advanced vaccines, only. These infections demand the adoption of flexible disease control strategies, based on the pursuit of different types of immune response. These may include increased immunocompetence for environmental pathogens, protective tolerance, improved control of the inflammatory response, maturation of innate immune responses (Horowitz et al., 2011). These new approaches should be supported by proper breeding strategies for disease resistance (Mallard et al., 2015) and by predictive clinical immunology assays of innate immunity. These can indicate a disease risk as a result of a negative imprinting of the innate immune system by environmental and metabolic, non-infectious stressors.

Conflict of interest

The authors declare there is no conflict of interest.

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