Evaluation of the Effectiveness of Comprehensive Prevention and Control Measures for Respiratory Diseases in Pig Farming

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Abstract: *All the causes of porcine respiratory diseases are the result of the combination of many pathogens and environmental factors. This paper examines the mechanism of immune evasion caused by the co-infection of porcine reproductive and respiratory syndrome virus and porcine circovirus type 2. It can be seen that ammonia is damaging to the mucous membrane, and high temperature and humidity are also harmful factors; a high stocking density may cause such damage. The three goals of this paper are air purification, reform of the immunisation programme and feed additives. Based on the previous analysis of morbidity, pathogen elimination efficiency, growth and treatment costs, interrupted time series analysis, nonlinear decay curve fitting and the marginal benefit net present value method have been used in this paper to obtain technical parameters for evaluating the effectiveness of prevention and control measures.*

Keywords: *Porcine respiratory disease, Multi-pathogen co-infection, Aerodynamic transmission, Immunization program restructuring, Elimination efficiency, Marginal benefit*

Introduction

Porcine Respiratory Disease Complex (PRDC) in pigs is a serious disease that can reduce production efficiency and increase treatment and economic losses. Etiological studies have found that the co-infection rate of porcine reproductive and respiratory syndrome virus (PRRSV), porcine circovirus type 2 (PCV2) and other opportunistic pathogens in affected populations is more than 60%, and at the same time, environmental physical factors (ammonia, temperature and humidity, dust) and high-density housing conditions are also promoting the airborne transmission of pathogens and damage to the mucosal barrier. Although many vaccines, additives and environmental control measures have been used in production, their specific synergy and quantitative differences in effect have not been studied; thus, the selection of prevention and control plans is currently based on limited information. Therefore, we need to continue to carry out extensive research on the pathogenesis and pathogenic ecological environment of this disease all the time, build a multi-target intervention system that includes source control, immunomodulation and local defence, and based on this, construct a multivariate quantitative evaluation model to increase the efficiency and economic feasibility of PRDC prevention and control. First, this paper will introduce the cooperative pathogenesis of pathogens, the pathway of environmental pollution and the density of transmission. Next, the three main technical trunks of air purification, optimisation of the immunization programme and feed additives will be combined, and finally, all the effects over time will be quantified by means of time-series analysis, decay curve fitting and marginal benefit fitting.

1. Analysis of the Pathogenic Ecology and Inducing Factors of Porcine Respiratory Diseases

1.1 Synergistic Pathogenic Mechanism of Co-infection by Major Pathogenic Bacteria and Viruses

The pathogenic spectrum of porcine respiratory disease complex (PRDC) is a type of multi-pathogen co-infection. Co-infection with porcine reproductive and respiratory syndrome virus (PRRSV) and porcine circovirus type 2 (PCV2) interferes with the interferon signalling pathway and thus reduces the phagocytosis and clearance functions of alveolar macrophages. Immune evasion has created a good microecological environment for the secondary invasion of opportunistic pathogens such as Streptococcus suis and Haemophilus parasuis, and a pathogenic chain with synergistic

amplification of viruses and bacteria has been formed. Research on the dynamics of infection has shown that after the first infection by a virus, the production of adhesion molecules in the respiratory epithelium increases several times, and thus bacteria can attach to the cells more easily. According to the latest single-cell sequencing data, the functions of different subpopulations of alveolar macrophages are changed after co-infection. Among these subgroups, the phagocytic index of the CD163-high expression group is reduced by more than 70%, and this group is also one of the main replication sites for PRRSV[1].

At the molecular level, the joint activity of pathogens is to spread virulence genes among themselves and suppress the inflammatory response of the host. Nsp2 is a non-structural protein of PRRSV that promotes the production of excessive IL-10 by the host to suppress the Th1-type immune response and prolong the period of bacterial infection. At the same time, bacterial lipopolysaccharide and viral double-stranded RNA can cross-activate NF-κB through TLR4 and TLR3, thus causing an excessive cytokine storm. This cascade reaction will increase the number of inflammatory cells in the lungs and cause irreversible damage to the alveolar epithelial-capillary barrier; thus, it will be the focus of the next round of prevention and control efforts. Cross-species comparative transcriptomics has shown that the expression of matrix metalloproteinases (MMP-9 and MMP-12) in the lung tissue of co-infected pigs is more than five times higher than in single-infected pigs, and this directly degrades collagen IV and elastin to promote the development of emphysema-like lesions.

1.2 Degradation Path of the Respiratory Mucosal Barrier by Environmental Physical Factors

An increase in the concentration of ammonia in the barn will reduce the ciliary beat frequency of the nasal and tracheal mucosa. Ammonia dissolves in the mucus layer to create a weak alkaline environment, alters the glycosylation structure of mucin, and thus reduces the binding ability of mucin for aerosol particles. After a long time in the presence of ammonia (more than 25 ppm), there is a decrease in the expression of tight junction proteins (claudin-1 and occludin) in the mucosal epithelial cells, an increase in paracellular permeability, and thus pathogens can cross the mucosal immune barrier and invade the underlying tissues. A drop in temperature will cause cold stress, reduce blood flow to the mucous membrane, and therefore decrease the secretion of local IgA. According to all kinds of experiments, repeated exposure to a cold environment can reduce the density of the subepithelial capillary network in the nasal turbinate mucosa by about 30 per cent and thus cause a local ischaemic injury.

Relative humidity and dust load are also a combination of two bad factors. A low-humidity environment (less than 40%) is harmful to health; there will be less water in the mucus, it will be thick, and thus mucociliary clearance will be impaired. When the relative humidity is over 80%, there will be an increase in airborne feed dust and dander particles that carry microorganisms and are harmful if inhaled. Pathogens in these particles can reach the alveoli and are therefore out of the defence range of the upper respiratory tract. Endotoxin activity on the surface of the particles can also activate the NLRP3 inflammasome in alveolar macrophages and therefore reduce the mucosal immune response induced by vaccination. According to the analysis of the distribution of aerosol particle sizes, at a relative humidity of 75%, the mass median aerodynamic diameter of PRRSV-positive particles is as low as 1.5 μm compared with 2.8 μm, and thus they are more likely to reach the alveoli. Humidifiers can reduce the proportion of such fine particles by 40% and keep the physical filtration function of the mucosal barrier[2].

1.3 Threshold Association of Stocking Density and Aerodynamic Transmission

The Effect of Stocking Density per unit area on the Airborne Transmission Efficiency of Pathogens is not linear. If the floor area per pig is less than 0.6 square metres, then the concentration of individual exhaled aerosols in the environment will exceed the dispersion capacity of the ventilation system. Based on the results of the computational fluid dynamics simulation, at high-density conditions, the lateral diffusion distance of aerosols between adjacent pens is less than 0.8 metres, and the probability of direct pathogen transmission by droplet nuclei among adjacent pens has increased threefold. A low transmission density will reduce the effective dose of the virus, and if it is below a certain threshold, the spread of infection will cease. According to the Lagrangian particle tracking model, increasing the density of 0.1 pigs per square meter will increase the crossing flux of droplet nuclei between pens by about 0.45 log10 copies per cubic meter per hour.

Stocking density will affect the spread of disease in animals and change how susceptible the

animals are to infection. Prolonged stress in a crowded place will increase the level of cortisol in the blood by activating the hypothalamic-pituitary-adrenal axis and reduce the proliferation of peripheral blood lymphocytes. Crowded behaviour increases the number of direct nose-to-nose contacts among people, and thus, the level of pathogens in oral and nasal secretions is high enough for direct transmission through contact. Based on the calculation of the airborne basic reproduction number (R0) model, if the stocking density exceeds 0.2 pigs per square meter, then the transmission index of PRRSV will be greater than 1.0, and thus there is a high risk of a population-level epidemic. Set an upper limit for the stock and avoid chemotherapy in that case. According to the extended dose-response meta-analysis, it is expected that a reduction of the pig density by 0.05 per square metre will decrease the population R_0 value by 0.22 (95% CI: 0.15-0.29), and this effect will be relatively stronger in winter when the ventilation rate is low. Build a density-ventilation coupling model to find the upper bound of the safe stocking density at different times of the year and then set good management operating limits.

2. Technical System for Multi-target Intervention in All-weather Disease Prevention and Control

2.1 Source Control Strategy for Air Purification and Aerosol Reduction

The number of pathogens in the indoor air particles will directly affect the transmission and spread of respiratory diseases. Droplet nuclei with a particle size of 0.3-5 μm can be reduced by two orders of magnitude in terms of nucleic acid copy number per unit volume of air with the combination of electrostatic adsorption and high-efficiency particulate air (HEPA) filtration in an air purification device. The electrostatic pre-charging unit gives all the aerosol particles the same charge so that they do not aggregate and settle under the influence of gravity, and at the same time increases the collection efficiency of submicron particles by the HEPA filter. Auxiliary ultraviolet radiation (254 nm) can change the secondary structure of the viral nucleocapsid protein that has bound to the filter surface and thus reduce the risk of re-aerosolisation[3].

A negative-pressure ventilation system and local air guides can be employed together to form a gradient-pressure field for air flow. Lower the position of the exhaust vent to about 0.3-0.5 metres from the ground so that the emitted aerosol can disperse quickly and is not concentrated in the adjacent pens. Low-concentration ozone injection (below 0.05 ppm) can oxidize and decompose ammonia and hydrogen sulfide, change the shape of viral envelope glycoproteins, and thus affect them. The concentration window will not reduce the ciliary clearance function of the porcine respiratory mucosa substantially, and therefore it will not affect the balance threshold for pathogen reduction and host defence.

2.2 Dynamic Balance of Cellular Immunity and Humoral Immunity in the Restructuring of Immunisation Programmes

The previous method of vaccination is to produce antibodies in the blood. PRRSV is an immunosuppressive virus, so a high level of humoral immunity can increase the degree of antibody-dependent enhancement (ADE). Staggered vaccination will be carried out for inactivated vaccines and live-attenuated vaccines at different times according to this study. First, the live vaccine is used to stimulate the clonal expansion of specific CD8+ T cells, and then the inactivated vaccine is employed to maintain the homeostasis of the memory B cell pool. Sequential vaccination will increase the proportion of IFN-γ-producing effector T cells in the alveolar lavage fluid and prevent the disruption of the immune response caused by excessive neutralisation of vaccine antigens with circulating antibodies.

The different types of adjuvants will lead to different kinds of immune responses (Th1 or Th2). A subunit vaccine that has been given a CpG oligonucleotide adjuvant can activate dendritic cells via the TLR9 pathway to promote the production of Th1 cytokines (IL-12 and IFN-γ) and strengthen the body's defence against intracellular pathogens. Aluminum adjuvants are of the type that promotes a Th2 response; although they can increase IgG levels, they do not promote the development of resident memory T cells in the respiratory mucosa. The two goals of the immunological indices are to reduce both the indicators of cellular immunity (CD4+/CD8+ ratio) and those of humoral immunity (geometric mean titer of neutralizing antibodies) at the same time; thus, they hope to reduce the immunopathological damage caused by an excessive single response and plan vaccination strategies[4].

2.3 Regulatory Mechanism of Respiratory Local Immunity by Feed Additives

Functional feed additives can affect the state of distal respiratory immunity in the gut-lung axis indirectly. Sodium butyrate is a type of short-chain fatty acid that can enter the blood, bind to the GPR41 receptor on the surface of alveolar macrophages, inhibit the activity of histone deacetylase, and thus increase the gene expression of the antimicrobial peptide cathelicidin. Every day, 500mg/kg of coated sodium butyrate was given to the pigs, and both the lysozyme activity of the bronchoalveolar lavage fluid and its in vitro bactericidal effect on Haemophilus parasuis increased. Active components of plant extracts (such as thymol and carvacrol) can enter the glycoprotein network of respiratory mucus and directly affect the Nrf2-ARE pathway in epithelial cells to increase the production of glutathione peroxidase and reduce damage to the ciliary structure caused by oxidative stress.

Yeast cell wall-derived β-glucan can be taken up by microfold cells in Peyer's patches, and then it is transported to bronchus-associated lymphoid tissue via the lymphatic system. Dectin-1 is the receptor for the binding of β-glucan and complement receptor 3 (CR3), and therefore the transepithelial transport of secretory IgA is promoted. Local immunomodulation does not need to be done systemically, so there will be no harm to the gut microbiota from prolonged antibiotic use. Metabolomics has shown that a certain combination of additives (co-formulation of *Clostridium butyricum* and astragalus polysaccharide) can change the structure of the glycocalyx on the surface of the respiratory mucosa and increase the expression level of sialyl Lewis X antigen; thus, it is hoped that pathogen adhesins will not bind to epithelial receptors.

3. Quantitative Evaluation Model of the Effectiveness of Prevention and Control Measures Based on Multiple Indicators

3.1 Time Series Intervention Analysis of Morbidity and Mortality

Model the change in the trend of population morbidity before and after the intervention in Section 3 using an interrupted time series model. Take the time when the intervention was carried out as the division point, and fit both the pre-intervention morbidity trend line and the post-intervention level shift and slope change. The model will not be affected by changes in seasons or the natural decline of the population's immunity, so it will show the general effect of all prevention and control measures. A population risk model in the form of Poisson regression is used for the mortality data, the daily death count is taken as the response variable, and lagged morbidity is employed to account for the time-lag effect of the natural course of the disease on mortality risk[5].

The autocorrelation structure of the segmented regression should be checked using the cumulative periodogram and the Ljung-Box statistic. If the residuals are an ARMA process, then autoregressive terms need to be added to correct for the bias in parameter estimation. Newey-West heteroskedasticity and autocorrelation consistent standard errors are used to correct for the problem of statistical significance in the intervention effect. To estimate the dynamic treatment effect, a counterfactual prediction method is used to increase the expected morbidity after the intervention based on data before the intervention, and then the cumulative difference between the actual observed values and the predicted values (that is, the absolute effect size) is calculated. The accumulated difference divided by the mean pre-intervention morbidity can be expressed as a relative effect percentage, and then the relative strengths of the prevention and control measures in different production units can be compared.

3.2 Calculation of Elimination Efficiency Based on the Pathogen Load Decay Curve

According to the gathered data of viral load at various times and the fitting of a nonlinear mixed-effects model, determine the elimination efficiency of the pathogen. Collect nasal swab or oral fluid samples from the same pig herd at different times after treatment and then quantify the copy number of pathogen nucleic acid in real time with qPCR. The first-order exponential decay function for the load with time is given by $C(t) = C0 \cdot e^{(-kt)}$, where C0 is the initial load and k is the elimination rate constant. Half-life ($t1/2 = \ln 2/k$) is the time a pathogen remains in the host, and it can be used to determine how quickly it is reduced. A random-effects model assumes that there is random variation among individuals in the estimation of fixed-effect parameters (k and C0), and it can also account for the intra-group correlation of repeated measurement data.

All the elimination rate constants of the combinations of the prevention and control measures can be compared with a likelihood ratio test. PRRSV is a chronic disease that can cause prolonged infection,

so a biphasic decay model (rapid phase + slow phase) has a better goodness of fit than a mono-exponential model. First, there will be a decrease in the number of free viruses and other viral particles; second, the quantity of latent or replication-restricted viruses will also decrease. The population-level index of elimination efficiency is the standardised difference in the elimination rate constant of the intervention group and the control group (Cohen's d effect size). If the size of this effect is greater than 0.8, then the two groups are considered to be very different. The area under the pathogen load curve (AUC) is the integral of the initial load and the clearance rate; thus, a small AUC indicates that the duration of infection is short and the risk of transmission is low.

3.3 Marginal Benefit Fitting of Growth Performance Parameters and Treatment Cost Savings

Respiratory diseases reduce a person's appetite and increase the basal metabolic rate because of reduced food utilisation. The parameters of growth performance (average daily gain and feed conversion ratio) are related to the degree of the disease (clinical scores). Piecewise linear regression is employed in this paper to find the point at which the daily increase in gain begins to slow down significantly after the clinical score reaches a certain level. Prevention and control measures are taken as the treatment variable, the non-intervened group is the reference group, and the increase in the average daily gain (ΔADG) of the treatment group over the entire finishing period is calculated. Multiply the increase by the number of finishing days and the unit price of live pigs to get an estimate of the direct benefit from growth promotion.

Treatment expenses refer to the cost of veterinary drugs, labour time for veterinary services and direct economic losses from death and culling. The daily treatment cost per pig is the dependent variable of this study, and a cost function will be built based on the morbidity rate, the duration of the disease and the unit price of drugs. The implementation of the prevention and control measures will reduce the proportion of cases and thus decrease the number of necessary treatments. Add the increase in growth performance and the decrease in treatment costs of the added part to the sum of marginal benefits, and then subtract the input costs of prevention and control measures (equipment depreciation, additive procurement, vaccine and adjuvant costs) using the net present value method to obtain the net benefit per pig. All kinds of hypothetical situations (such as changes in the distribution of pathogens or fluctuations in feed prices) have been considered, and sensitivity analysis has been carried out to determine the confidence interval and break-even point of net benefit. Based on the fitting results, the final output indicator used to rank the economic feasibility of all combinations of prevention and control technologies is the marginal benefit rate (net benefit divided by prevention and control cost).

Conclusion

Systematically investigate the synergistic pathogenic mechanism of pathogen co-infection in porcine respiratory diseases, study the degradation pathway of the mucosal barrier by environmental physical factors, and determine the threshold association between stocking density and aerodynamic transmission. Based on the above, this paper has developed a three-target intervention technical system that covers air purification and aerosol reduction, restructuring of immunization programs, and local immune regulation by means of feed additives, and has also put forward several quantitative evaluation models, such as interrupted time series analysis of morbidity and mortality, calculation of elimination efficiency under the pathogen load decay curve, and marginal benefit fitting of growth performance and treatment costs. Therefore, the effect of all-encompassing prevention and control measures should be judged based on the combination of the three aspects of epidemiology, viral dynamics and economics, and the main assessment indicators will be the pathogen elimination rate constant and the marginal benefit rate. In the future, we will learn more about the functional heterogeneity of subsets of alveolar macrophages under co-infection conditions and their different responses to various interventions using single-cell multi-omics technology; develop intelligent environmental control systems that can dynamically adjust the density-ventilation coupling model in real time and issue early warnings when thresholds are exceeded; explore synergistic efficacy formulas for oral immunomodulators that target both the gut microbiota and respiratory local immunity; and build a longitudinal cohort database across production units to integrate and learn multi-source evaluation indicators through machine learning, thus improving the accuracy and generalizability of predictions for prevention and control effectiveness.

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