Strategy of the genome of viruses and bacteria and problems of immune prevention in industrial poultry farming

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Abstract. The article argues that the use of the phenomena of immunological resonance and the vaccine function of pathogenic bacteria inactivated by antibiotics multiple times increases the effectiveness of immunoprophylactic measures in industrial poultry farming. The timing of revaccinations has been established to ensure synchronization of the immunogenic effect of the vaccine antigen and anti-idiotypes of immunoglobulins of different classes. We also consider the process of pinocytosis as nonspecific phagocytosis.

1 Introduction

Every strategy involves development. Development is a solution to problems. When talking about the role of veterinary medicine in ensuring food security, the fight against infection comes to the fore.

Back in the 19th century, the English naturalist Thomas Robert Malthus, on whose work Charles Darwin relied, put forward a theory according to which humanity faces three problems at all times: incessant wars, epidemics and a decrease in soil fertility [9], the validity of which we are witnessing. Consequently, the main strategy of medicine and veterinary medicine should be aimed at combating epidemics and epizootics. This means that the correct determination of infection control strategies is a crucial task of veterinary medicine in ensuring food security. Moreover, this solves not only the problem of increasing livestock and poultry products, but also prevents a decrease in soil fertility, since manure and poultry droppings are the main sources of increasing humus in the soil. In addition, addressing food security reduces the likelihood of wars breaking out. It is not for nothing that the Dutch breeder was awarded the Nobel Peace Prize for developing the highest-yielding wheat variety, although this variety turned out to be unpromising in the future, as it requires super-intensive use of mineral fertilizers and pesticides.

Based on the foregoing, we believe that the fight against epizootics is of fundamental importance in solving universal human problems identified by Malthus. Veterinary science and practice should approach their responsibilities from such positions.

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The success of any struggle depends on the correctness of the adopted strategy, which in our case is impossible without knowledge of the strategy of the genomes of viruses and bacteria. However, this is an ambiguous task, since biological evolution, based on mutational and recombination variability is stochastic in nature, i.e. undetermined, nomogenesis absent. However, the emergence of a new thought, which also has a mutational nature, due to its puzzlement and algorithmically rapid flow, is capable of predicting the strategy of the genomes of viruses and bacteria.

However, despite the fact that optimistic judgments are being made in this direction [1, 11], the success of immune prevention of epidemics and epizootics remains problematic. We cannot yet offer more than an increase in the number and types of vaccinations.

Today's immunoprophylaxis is based only on lymphoid immunity. Constitutional and nonspecific phagocytic immunity remain out of sight. To substantiate this objection, we first of all refer to the classical experiments of Louis Pasteur. He found that bathing chickens in cold water will break the constitutional immunity that provides birds with natural immunity to the anthrax pathogen [4]. In addition, it is known that crosses of colored chickens are more resistant to the causative agent of Marek's disease [4].

For example, in the Uzbekistan-Germany joint venture "Agalyk Lomanparranda" it was stated that in workshops where the herd was stocked with pullets of different ages, the number of revaccinations against the causative agent of Newcastle disease was less than in herds stocked with pullets of the same age, as required by the procedure established throughout the world. The mechanism of this dilemma remains unclear. Or in the same "Agalyk Lomanparranda", when it was not possible to curb the salmonellosis enzootic by vaccination, the way out was to switch to breeding white chickens. During the formation of the poultry farm, we also initially bred only Loman-Brown. However, due to the increase in sporadic cases of salmonellosis, they were forced to switch to breeding crosses of white chickens. The mechanism of this dilemma remains unclear.

Therefore, in order to adopt an immunoprophylaxis strategy that is adequate to the strategies of the genomes of viruses and bacteria, it is necessary to highlight all the components of general anti-infective resistance and ways to enhance them. If we cannot do this or do not have time, then according to the theory of self-regulation of the epidemic process by V.D. Belyakov [6], the epidemic process will stabilize only after the formation of a sufficient immune background [10], which reflects the basic law of biological evolution - stabilizing selection, illuminated by Charles Darwin . However, self-regulation of the epidemic process is accompanied by huge losses, like the influenza pandemic, which claimed 18 million human lives, occurred exactly a hundred years ago in Europe and received the sonorous name - Spanish Flu, to the point that influenza became a way of coexistence between the virus and humanity. This is also evidenced by the current situation regarding Covid-19.

2 Materials and methods

The initial material was an analysis of the results of five years of monitoring of immunoprophylaxis of Newcastle disease in chickens in the Uzbekistan-Germany joint venture "Agalyk Lomanparranda".

The second material was information that in the same "Agalyk Lomanparranda" and in our poultry farm, higher resistance of white chicken crosses to salmonella was observed.

The third material was literary information about the impossibility of infecting chickens nutritionally even with highly virulent strains of Salmonella. [5,12].

The fourth material was a schedule of all types of vaccinations regulated in industrial poultry farming [5].

The adequacy of the immunoprophylaxis strategy to the strategies of the genomes of viruses and bacteria was assessed by indicators of productivity, safety and frequency of chicken vaccinations. To illuminate the mechanisms of formation of an adequate immune background, serological studies were carried out using the methods of RA, ChHAR, RPGA and ELISA. To determine the difference in the importance of immunoglobulins M and G in the development of the immune status of chickens, they were measured by the Mancini diffuse precipitation method.

The studies were carried out in the small poultry farm "Chimkurganparrandalari" in the Ishtykhan district, in the poultry house of the private LLC "MIRONQUL AGROZOOVETSERVIS ILMIY-AMALIY MARKAZI" Samarkand region, at the Department of Epizootology, Microbiology and Virology of the SamSUVM, in the laboratory of microbiology of SRIV, in the laboratory of helminthology of SRIV and in the laboratory of the clinic of the Institute of Medical Parasitology named after M.I. Isaev in Samarkand.

3 Results and Discussion

An analysis of the results of five years of monitoring of vaccinations against the causative agent of Newcastle disease of chickens carried out at Agalyk Lomanparranda showed that the number of revaccinations in different workshops is different, in some it is less, and in others it is more. For example, in the 10th workshop, only two revaccinations were carried out during the entire production cycle, while others had 3-4 or even 5-6. It is paradoxical that in the 10th workshop the herd was stocked with two populations of pullets, differing in age by one month, which is a violation of the requirements of the regulations for stocking the herd with pullets of the same age. When a comparative study of the number of revaccinations in same-age and uneven-age herds was carried out, it turned out that in all cases in uneven-age herds the number of revaccinations was less than in same-age herds (Table 1). Most importantly, the smallest number of revaccinations was among those of different ages for one month in the herd. At the same time, in workshops equipped with pullets of different ages for 15-20 days there were 3-4, and in workshops with pullets of the same age - 5-6. This paradox required theoretical and practical clarification.

Table 1. Comparative study of the number of revaccinations in same-age and mixed-age populations.

Indicators	Same age group (n=8)	Mixed age group (n=11)
1. Duration of immunity, days M±m	176±33.17	239±91.98
2. Number of vaccinations M±m	2.6±0.22	1.5±0.17

For theoretical understanding, we turned to the theory of idiotypic networks by K. Erne, according to which specific antibodies, i.e. idiotypes, due to their genetic heterology, act on the body's immune system, like antigens, initiating the production of anti-idiotypic antibodies, which reflect the specificity of the vaccine antigen. Practical confirmation of this phenomenon is manifested in the greatest effectiveness of revaccinations on the 28th day, which was also taken into account by Louis Pasteur in the immune prophylaxis of rabies in humans. The protocol for the revaccination schedule against Covid-19 at 28 days is based on this.

We believe that there is a direct connection between the greatest effectiveness of revaccinations on the 28th day and the smallest number of revaccinations when herds are mixed in age by one month, since pullets are vaccinated against Newcastle disease before transfer and when live vaccines are used, the release of the virus into the environment begins after a month. In this case, mutual infection with vaccine viruses can occur, which leads to an increase in the immune background leading to a decrease in the number of

revaccinations. Most importantly, when pullets of different ages are mutually infected with the released vaccine viruses, their antigenic actions synchronize with the antigenic action of anti-idiotypes that have accumulated by this time in the body of chickens, which leads to the phenomenon of immunological resonance.

To reliably confirm the presence of the vaccine property of anti-idiotypes, an experiment was carried out that was radically different in nature from infectious processes. For this purpose, gamma globulins from the blood serum of sheep isolated by the salivation method a month after vaccination against coenurosis with a vaccine made from the larvae of Multseps multseps sheep were vaccinated in intact sheep. As expected, by a month after vaccination, the accumulation of antibodies against Multseps multseps [3] in the passive hemagglutination reaction was detected in their blood serum, which confirmed the presence of antigenic properties in gamma globulins of Multseps multseps larvae.

We believe that it is the synchronization of the immunogenic actions of anti-idiotypes with the antigens of the vaccine or field virus, ascertained in herds of different ages, that leads to the phenomenon of immunological resonance, ensuring a reduction in the number of vaccinations.

However, the question still remained open as to what anti-idiotypes belonging to which class of immunoglobulins function in this.

To clarify this issue, an experiment was carried out on chicken embryos from the 14th day of prenatal life and on chickens from one day to one month of postnatal life.

It was found that in the last days of prenatal life and in the first days of postnatal life, IgM is primarily absorbed. IgG is absorbed mainly in the first week of postnatal life. This means that in chickens, by the 14th day, anti-idiotypic antibodies are classified as IgM, since by the seventh day their titer reaches a maximum and begins to act as antigens, initiating the synthesis of anti-idiotypes. Although idiotypes of the IgG class will have time to accumulate by the end of the first week, due to their two-dimensionality they have less antigenic power, anti-idiotypes of this class reach their maximum only by the 28th day, but due to the fact that they make up the bulk of antibodies they play a leading role in the formation of immunological resonance leading to a decrease in the number of revaccinations [2].

This was clearly expressed in the fight against the enzootic Marek's disease that occurred on our farm. We managed to curb this enzootic only after revaccination on the 28th day (Table 2).

Table 2. Curbing the enzootic Marek's disease.

Indicators	**Days and number of vaccinated chicks**		
	in 1 day (n=2500)	**on days 1 and 21 (n=2500)**	**on days 1 and 28 (n=2500)**
Amount of transit lameness	758	40	-

It is noteworthy that this enzootic also spread among a flock of rock pigeons living under the roof of unused premises. Most importantly, the enzootic occurred only after the transition to breeding crosses of white chickens, which confirms the resistance of crosses of colored chickens to Marek's disease. In addition, as a result of the enzootic, the reproduction of rock pigeons living under the roof of the poultry house has ceased. One pair's surviving pigeons were dark blue, even almost black.

All these results required scientific interpretation of the role of melanin in providing general anti-infective resistance. However, a paradoxical situation developed. The fact is that both in “Agalyk Lomanparranda” and in our country, the transition to breeding white chickens helped in curbing the enzootic salmonellosis, which cannot be associated with melanin, since white color does not mean weakness of melanogenesis in white chickens. First of all, we must keep in mind that melanin and the form of its manifestations in the

animal world are diverse and perform different functions. The complete absence of melanogenesis is called albinism, weakening is called albinoidism. It is well known that throughout the animal world, without exception, albinism and albinoidism are accompanied by a sharp decrease in vitality. However, the mechanism for ensuring high vitality by melanin remains unexplored. Only in physiological genetics is it revealed that between melanogenesis and tissue regeneration there is a struggle for sulfhydryl groups [7].

Indeed, in studies conducted in a completely different direction, it has been reliably proven that mitigating this fight slows down the graying of hair in people and even restores the melanization of graying hair. We have preliminary information about the existence of a connection between the positive effect of the herbal remedy Yarrow on the melanization of graying hair in humans and the safety and extension of the life of chickens from 20 to 26 months, with a cost-effective productivity of 75% at the end of the production cycle.

It is known that the infectivity of a pathogen is based on the affinity of the molecular receptors on the surface of the microorganism with the molecular receptors of the cells of the microorganism, which results in invasiveness. This means that pathogenicity is associated not only with the virulence of the infectious agent, but also with the sensitivity of the macro organism. This is central to the infectious process [9].

However, without the mutual affinity of molecular receptors of different taxa, sexual reproduction would not have arisen. Without this, multicellularity would not have appeared, histogenesis or organogenesis would not have occurred. This means that epidemics and epizootics are a payoff for removing obstacles from the road to progressive biological evolution [8].

The reason for such detached judgments around melanin was that we came across facts showing the presence of a strong connection between general anti-infective resistance and the state of melanogenesis in chickens.

The fact is that although in recent years we have completely switched to breeding white chickens, the enzootic salmonellosis still broke out. It is noteworthy that in one case this was expressed only in a sharp decrease in egg production without any clinical and pathological signs, in another case - an increase in the laying of eggs without shells. In the latter case, it was necessary to sell not only eggs, but also melange. It was reminiscent of paratyphoid abortion of sheep. This means that enzootic salmonellosis can manifest itself not only in the classically described form, with all the clinic pathological signs. We agree with the conclusion of medical infectologists that among all infections, salmonellosis has no equal in the complexity of its epidemiological and socio-ecological manifestations [12]. We know that both SamSUVM and SRIV have been conducting relentless research in this direction over the past 60 years. However, things are still here. All this requires finding the still unknown causes of salmonellosis enzootics and reducing general anti-infective resistance in order to develop appropriate measures to prevent them. Looking ahead, we will say that in today's unfavorable state of industrial poultry farming in the republic, salmonellosis occupies a leading place.

From these positions, we believe that salmonellosis, like all opportunistic pathogens, is also called a secondary, opportunistic, nosocomial infection, which requires considering poultry houses for egg production as a maternity hospital. In light of this position, it becomes clear that neither breeding white chickens nor vaccination alone will solve the problem.

The results of our studies showed that in all forms of salmonellosis enzootic manifestations, the root cause was an increase in pathological molting. It is noteworthy that the pathological molting was accompanied by a sharp increase in the chicken's irritability. There is information in the literature that molting sharply increases the bird's need for melanin. In experiments on rats, it was found that adding melanin to the diet reduces the excitability of afferent nerves and reduces the irritability of the animal.

When we strictly prevented cases of pathological molting, neither a decrease in productivity nor an increase in the laying of eggs without shells became a problem. Currently, we have a flock of chickens that is in the 12th month of the production cycle; for seven months, both productivity and safety have not yet fallen below 96%. Previously, in this segment of the production cycle, both productivity and safety did not exceed 85%. Most importantly, during these seven months there was no need for revaccination against Newcastle disease.

We learned that the main cause of pathological molting is a draft of damp, cold air. We believe that in this case, the classic experiment of Louis Pasteur shines through, which proved the possibility of breaking the constitutional immunity of birds by bathing chickens in cold water. It was also noteworthy that chickens of colored crosses were less susceptible to pathological molting. We believe that melanin plays a positive role by reducing the affinity of the molecular receptors of the microbe and the host.

Another conceptually new result of our research was that the use of an adequate course of treatment of chickens in chicken flocks unaffected by salmonellosis with the antibiotic Oxy-dox made it possible to curb the enzootic salmonellosis, accompanied by both a decrease in egg production and an increase in the laying of eggs without shells. In the first case, productivity, which had decreased in a short period of time from 90% to 60%, was restored to 83%; in the other, the laying of eggs without shells became sporadic. Based on these results, we were able to prevent the development of the onset of enzootic disease, which manifests itself in an increase in the incidence of disease in chickens from two weeks of age. At the same time, it was established that the use of a full course of the antibiotic Oxy-doxy gives not only a therapeutic, but also an immune prophylactic effect, since the enzootic disease was completely prevented.

The similarity of the results of all studies testing the effect of the antibiotic became the basis for putting forward the concept according to which pathogenic bacteria of birds, inactivated by the antibiotic, perform a vaccine function and initiate the formation of long-term active immunity, triggering the functioning of the idiotypic network according to K. Erne. Most importantly, active immunity is formed against infectious pathogen strains on the farm.

We believe that this is a contribution to the theory and practice of designing enteral vaccines. This means that we should not be talking about something that does not explain anything without the systemic use of antibiotics. It is necessary to clarify both the therapeutic and dysbacteriotic consequences and their immune prophylactic significance in the light of our proposed concept of the vaccine function of pathogenic bacteria in the body of chickens inactivated by an antibiotic.

Another conceptually new approach to the problems of immune prophylaxis in industrial poultry farming is to highlight the role of pinocytosis in ensuring general anti-infective resistance.

Nevertheless, the decisive arguments were the presence of cross differences in favor of white crosses in terms of general anti-infectious resistance; antibody titers in the blood serum against Salmonella in RA, against NB in ChHAR and against IB in ELISA.

Finally, an analysis of the vaccination schedule currently regulated in industrial poultry farming showed that the immune prophylaxis strategy, which ensures the coexistence of micro- and macro organisms without negative consequences, is based only on lymphoid immunity and is different in relation to various infectious agents [13]. For example, for Marek's disease, a single dose at one day of age is considered sufficient, for Gambaro disease, twice during the first month of the chickens' life, for smallpox and ILT 3-4 times, for NK and IB 5-6 times vaccinations per production cycle. Moreover, in the case of Newcastle disease, constant monitoring of immunity intensity and immediate revaccination are required if the intensity is below 80%.

It is believed that the sufficiency of a single vaccination for Marek's disease is based on the possibility of coexistence of the virus and birds in a persistent form without negative consequences due to the immune background. At the same time, to prevent the danger of increasing the virulence of the field virus, a more effective version of the vaccine is designed every 15-20 years.

In the regulated schedule, in no case do the timing of revaccinations coincide with the phenomenon of immunological resonance occurring on the 14th and 28th days, which is why the total number of revaccinations during the production cycle becomes large.

As for the immune prophylaxis of bacterial infections, for which vaccination is not regulated, remains unclear. It is known that in practice, when vaccinating chickens against Marek's disease at one day of age, gentamicin is used unofficially. A full course of any new antibiotic is also unofficially recommended. We believe that this in an unintentional way triggers the vaccine function of pathogenic bacteria in the body of chickens inactivated by antibiotics.

We believe that taking into account the phenomenon of immunological resonance in adjusting the vaccination schedule, which is currently regulated multiple times in industrial poultry farming, reduces the number of revaccinations during the production cycle. Timely application of the phenomenon of the vaccine function of pathogenic bacteria in the body of birds, inactivated by antibiotics, eliminates the need for artificial vaccinations.

4 Conclusion

- The strategy of the genomes of viruses and bacteria is aimed at acquiring the right to coexist with the macro organism.
- The immune prophylaxis strategy is designed to ensure coexistence with the infectious agent without negative consequences.
- Coexistence with infectious agents without negative consequences is possible only with the development of a sufficient immune background and the potential for general anti-infective resistance.
- In the formation of the immune background, a powerful lever is the phenomenon of immunological resonance. The vaccine antigen is synchronized on the 14th day with IgM anti-idiotypes, on the 28th day IgG.
- The use of the phenomenon of the vaccine function of pathogenic bacteria in the body of chickens, inactivated by an antibiotic, completely eradicates the enzootic condition of opportunistic bacteria and eliminates the use of vaccines.
- Pinocytosis of avian intestinal epithelial cells should be considered as nonspecific phagocytosis.
- Melanin reduces the affinity of the molecular receptors of the microorganism with those of the cells of the macro organism.
- The immune prophylaxis strategy should take into account both constitutional and lymphoid immunities, as well as nonspecific potencies of general anti-infective resistance in the form of pinocytosis.

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