MOHAMMED V UNIVERSITY IN RABAT
National School of Computer Science and Systems Analysis

A THESIS

Submitted in partial fulfillment of the requirements for the degree of

Research Master in Bioinformatic and Complex Systems Modeling Applied to Healthcare

Subject:

Prediction of the optimal age for vaccination against H9N2 in chickens using mathematical modeling

Submitted by:

BASRI Rania

8 July 2023

Members of the jury:

Pr. Azize KOUR	President	ENSIAS – Rabat
Pr. Noha EL KHATTABI	Examiner	UM5 – Rabat
Pr. Saadia NASSIK	Supervisor	IAV Hassan II – Rabat
Dr. Amal ESSALAH-BENNANI	Supervisor	CEVA Santé Animale
Pr. Mounia ABIK	Supervisor	ENSIAS – Rabat
Pr.Mohamed NAOUM	Supervisor	ENSIAS - Rabat

Acknowledgement

This work would never have been realized without the contribution of several people and institutions to whom I would like to express my greatest and sincere gratitude.

I am extremely grateful to my supervisor **Prof. NAOUM Mohamed** for his unwavering leadership, invaluable insight, and continued encouragement. His expertise and guidance have been instrumental in defining my research direction and honing my analytical skills

I am very grateful to **Prof. ABIK Mounia** for her time and effort in providing feedback, reviewing drafts, and participating in meaningful discussions.Her constructive criticism and thought-provoking insights helped me refine my ideas and improve the quality of this project.

I would like to express my heartfelt thanks to **Prof. NASSIK Saadia**, Professor at the Rabat Institute of Agronomy and Veterinary Medicine. Her confidence, invaluable advice and key operational insights made this work possible. Furthermore, I am very grateful to **Dr. ESSALAH-BENNANI Amal** for her valuable help, support and assistance throughout the project.

Furthermore, I would also like to acknowledge with much appreciation the members of the jury **Prof. KOUE Azize** and **Prof.EL KHATTABI Nouha** for taking the time and effort to evaluate this work.

Finally, I want to sincerely thank my friends and family for their unfailing love, support, and encouragement during my academic career. They have been a constant source of motivation since they have faith in my talents. I sincerely appreciate their support in my life and the courage they have given me to face obstacles and achieve my academic objectives. I appreciate you standing by my side as my rock.

Résumé

Le succès du programme de vaccination contre la grippe aviaire H9N2 chez les poulets de chair repose sur divers facteurs, dont la date de vaccination joue un rôle crucial. L'objectif de ce projet est de modéliser la décroissance des anticorps d'origine maternelle (AOM) chez les poulets de chair afin d'évaluer leur niveau à différents moments clés. Cela permettra de déterminer la date optimale de vaccination en fonction du niveau d'anticorps mesuré le premier jour (Jour 1).

L'équipe de recherche de l'Unité de Pathologie Aviaire de l'Institut Agronomique et Vétérinaire Hassan-II ont collecté deux bases de données. La première base de données contient les titres d'AOM sans vaccination de 20 poussins à différentes étapes de leur développement (1, 7, 14, 21, 28, 35, 42 jours), tandis que la deuxième base de données contient les titres d'AOM avec vaccination à différents intervalles de temps (1 jour, entre 5 et 7 jours, et enfin 14 jours) aux mêmes moments clés (1, 7, 14, 21, 28, 35 jours). Les mesures ont été réalisées à l'aide des kits ELISA FLUNPS/ELISA et FLUH9S/ELISA.

Dans ce projet, deux modèles mathématiques ont été utilisés. Le premier modèle est basé sur la représentation de la dégradation des anticorps en utilisant une fonction exponentielle et un seuil de coupure (cut-off), tandis que le deuxième modèle est un problème d'optimisation qui prend en compte à la fois la dégradation des anticorps et la réponse immunitaire , spécifiquement pour le kit FLUNPS.

Le premier modèle a montré que la plupart des poussins ont atteint le niveau d'activité des anticorps requis en environ 19 jour, avec un maximum 20 jour pour le kit FLUH9S et 18 jours, avec un maximum de 18 jours pour le kit FLUNPS. En revanche, le deuxième modèle a indiqué que 21 jours constitue l'âge optimal pour la vaccination, avec un niveau d'anticorps estimé à 596 unités pour le kit FLUNPS.

Ces résultats soulignent l'importance de l'analyse approfondie des modèles et de l'évaluation de leur performance pour prendre une décision éclairée sur le moment optimal de la vaccination contre la grippe aviaire H9N2 chez les poulets de chair.

Mot clé : Grippe aviaire H9N2 ; Poulets de chair ; Modélisation mathématique ; Âge optimal de vaccination ; Seuil de coupure

Abstract

The success of the H9N2 avian influenza vaccination program in broilers depends on a number of factors, of which the date of vaccination plays a crucial role. The aim of this project is to model the decay of maternally derived antibodies (MDA) in broilers in order to assess their levels at different key times. This will enable the optimum date for vaccination to be determined on the basis of the level of antibodies measured on the first day (Day 1).

The research team of the Avian Pathology Unit of the Hassan-II Agronomic and Veterinary Institute collected two databases. The first database contains the AOM titers without vaccination of 20 chicks at different stages of their development (1, 7, 14, 21, 28, 35, 42 days), while the second database contains the MDA titers with vaccination at different time intervals (1 day, between 5 and 7 days, and finally 14 days) at the same key moments (1, 7, 14, 21, 28, 35 days). The measurements were carried out using the FLUNPS/ELISA and FLUH9S/ELISA kits.

Two mathematical models were used in this project. The first model is based on the representation of antibody degradation using an exponential function and a cut-off point, while the second model is an optimization problem that takes into account both antibody degradation and the immune response, specifically for the FLUNPS kit.

The first model showed that most chicks reached the required level of antibody activity in around 19 days, with a maximum of 20 days for the FLUH9S kit and 18 days, with a maximum of 18 days for the FLUNPS kit. In contrast, the second model indicated that 21 days was the optimal age for vaccination, with an estimated antibody level of 596 units for FLUNPS kit.

These results highlight the importance of thorough analysis of the models and evaluation of their performance to make an informed decision on the optimal timing of vaccination against H9N2 avian influenza in broilers.

Key words : Avian influenza H9N2; Broilers; Mathematical modeling; Optimal vaccination age; Cut-off threshold

List of Abbreviations

AI	Avian influenza virus
MDA	Maternal-Derived Antibodies
HA	Hemagglutinin
NA	Neuraminidase
CMTC	Continuous-Time Markov Chain
DMTC	Discrete-Time Markov Chain
HIA	Hemagglutination Inhibition Assay
ELISA	Enzyme-Linked Immunosorbent Assay
RSSR*GLF	Recommended Swing Speed Range* Gay Liberation Front

List of figures

List of tables

Table of content

Chapter1: General introduction

This chapter serves as a comprehensive introduction to the thesis, providing an overview of the research context, the problem statement, and an outline of the thesis structure.

1. Background and motivation

According to the Ministry of Agriculture, Maritime Fisheries, Rural Development and Waters and Forestry, the poultry sector plays an important role in creating jobs and contributing to ensuring food security for animal protein in Morocco. The sector is also characterized by its strong export and foreign market penetration, particularly in Africa. In 2019, exports of poultry products reached 2,000 tons (chicks and hatching eggs)

In January 2016, low pathogenic avian influenza subtype H9N2 was first detected in poultry in Morocco[1].In response, the National Sanitary and Security Food Office (ONSSA) authorized emergency vaccinations for all types of poultry production. This proactive measure aimed to control the spread of the virus, protect poultry populations, and minimize economic losses. The collaboration between ONSSA, poultry producers, and stakeholders was crucial in implementing the emergency vaccination program. This demonstrated Morocco's commitment to preserving animal health and ensuring the sustainability of the poultry industry.

This project is motivated by a problem encountered by the Hassan II-Rabat Agronomic and Veterinary Institute (IAV) for the vaccination of broilers. It should be noted that we do not have many studies that have dealt with the problem of the effectiveness of vaccination strategies for poultry, so it will push us even more to carry out this project in order to improve the poultry sector of our country.

2. Problematic and objective

Vaccination against H9N2 avian influenza is a crucial measure for preventing the spread of the disease and protecting poultry, particularly broilers. However, the presence of pre-existing antibodies, whether of maternal origin or due to previous exposure to the virus, poses a major challenge to the effectiveness of vaccination. These maternal antibodies interfere with the vaccination process, reducing vaccine efficacy and compromising the immune response. This raises concerns about the inability of vaccination to provide adequate protection against H9N2 avian influenza in chickens.

The problem therefore lies in finding the best time to vaccinate broilers in order to circumvent the inhibitory effect of maternal antibodies and optimize vaccine efficacy. The first few days of the chicks' lives, as well as the period following the reduction in maternal antibodies, are critical times when vaccination can be compromised. It is therefore essential to determine the optimum vaccination period to maximize the immune response and ensure effective protection against H9N2 avian influenza.

With this in mind, mathematical modeling is proving to be an indispensable tool for studying and predicting the dynamics of the immune response to vaccination. By using mathematical models, it is possible to take into account key factors such as the age of the chicks, the degradation of maternal antibodies and the evolution of the immune response, in order to gain a better understanding of the biological mechanisms involved. This approach makes it possible to formulate explicit hypotheses and predict the efficacy of vaccination at different periods, providing valuable information for the development of optimal vaccination strategies.

The aim of this research is therefore to determine the optimal date for vaccination against H9N2 avian influenza in broilers using mathematical models and data collected by the the Hassan II-Rabat Agronomic and Veterinary Institute (IAV). By combining mathematical models with empirical data, this study aims to optimize the vaccination strategy, by identifying the most favorable period for an optimal immune response and effective protection against H9N2 avian influenza in broilers. The results obtained will help to improve vaccination practices and enhance poultry health in the context of H9N2 avian influenza.

3. Methodology

As part of this project, I decided to adopt a methodical process for carrying out the mathematical modeling. The choice of this approach ensures a structured and rigorous approach to solving the problem posed. This process comprises five key stages (figure1):

- Posing a Problem : define clearly the problem and identify specific research questions

- Making Assumptions: Establish hypotheses based on existing knowledge and available information and identify key factors.

- Building a Model: involves formulating equations, relationships or mathematical rules that describe the system or phenomenon under study. These mathematical models represent the interactions and behaviors of the system in a simplified and abstract way, making it easier to analyze and understand the problem.

- Analyzing and Revising the Model: This iterative phase enables the model to be progressively refined, guaranteeing its relevance and validity for decision-making or the study of the phenomenon under study.

- Validation and use of the model: is an essential step in guaranteeing its reliability and usefulness in practice.

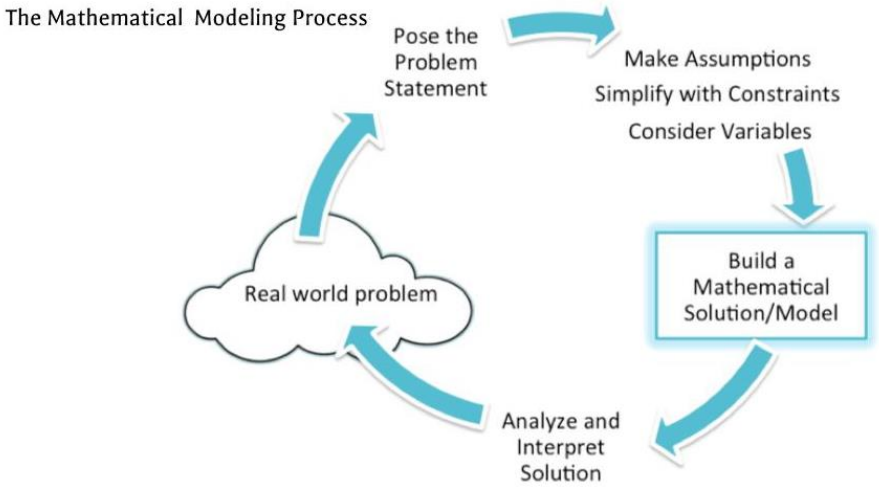

Figure 1 : Mathematical Modeling Process

4. Thesis outline

The rest of this project will be organized as follows:

- Chapter 2: provides detailed information on the H9N2 virus, including its classification, genetic structure, and mode of transmission, impact on avian health and prevention and control measures in place.

- Chapter 3: presents a literature review of previous studies that have addressed the issue of determining the optimal age for vaccination using mathematical modeling. It examines the different approaches, methods and models used in these studies, as well as the results obtained.

- Chapter 4: describes in detail the mathematical modeling methodology used to determine the optimal age for vaccination against the H9N2 virus.

Chapter 2: Virus H9N2

This chapter looks at the H9N2 avian influenza virus. We present its characteristics, its impact on avian health and industry, and control strategies. This chapter aims to deepen our understanding of the virus and highlight its importance for health and disease prevention.

1. Introduction to the H9N2 virus

Avian influenza is a disease resulting from a viral infection of avian influenza type A genus of the Orthomyxoviridae family[2]–[5]. It has different subtypes that are determined by the antigenic variations in the two glycoproteins found on the surface:

- ***Hemagglutinin (HA)*** : attaches virions to cells by binding to terminal sialic acid residues on glycoproteins/glycolipids to initiate the infectious cycle.[6]
- ***Neuraminidase (NA):*** cleaves or breaks the bonds between the viral particles and the terminal sialic acid residues on the surface of infected cells or on newly formed virions. .[6] This cleavage allows the released virions to complete their infectious cycle by separating from the host cell and spreading to infect other cells.

Subtype	Virus found in species of origin[a]			
	Humans	Swine	Horses	Birds
HA				
H1	PR/8/34	Sw/Ia/15/30	–[b]	Dk/Alb/35/76
H2	Sing/1/57	–	–	Dk/Ger/1215/73
H3	HK/1/68	Sw/Taiwan/70	Eq/Miami/1/63	Dk/Ukr/1/63
H4	–	–	–	Dk/Cz/56
H5	–	–	–	Tern/S.A./61
H6	–	–	–	Ty/Mass/3740/65
H7	–	–	Eq/Prague/1/56	FPV/Dutch/27
H8	–	–	–	Ty/Ont/6118/68
H9	–	–	–	Ty/Wis/1/66
H10	–	–	–	Ck/Ger/N/49
H11	–	–	–	Dk/Eng/56
H12	–	–	–	Dk/Alb/60/76
H13	–	–	–	Gull/Md/704/77
H14	–	–	–	Dk/Gurjev/263/82
NA				
N1	PR/8/34	Sw/Ia/15/30	–	Ck/Scot/59
N2	Sing/1/57	Sw/Taiwan/70	–	Ty/Mass/3740/65
N3	–	–	–	Tern/S.A./61
N4	–	–	–	Ty/Ont/6118/68
N5	–	–	–	Sh/Austral/1/72
N6	–	–	–	Dk/Cz/56
N7	–	–	Eq/Prague/1/56	FPV/Dutch/27
N8	–	–	Eq/Miami/1/63	Dk/Ukr/1/63
N9	–	–	–	Dk/Mem/546/74

[a] The reference strains of influenza viruses, or the first isolates from that species, are presented.
[b] –, not found in this species.

Table 1 : HA and NA subtypes of influenza A viruses isolated from humans, lower mammals, and birds **[2]**

From the table 1 we distinguish that there's 16 subtypes numbered H1 to H16 and 9 subtypes numbered N1 to N9 and all combinations are possible between the different protein subtypes.

In terms of virulence characteristics, influenza viruses can be categorized into two main groups. The first group includes highly pathogenic avian influenza viruses (HPAI), which typically possess the H5 or H7 subtype of HA and exhibit high virulence in poultry. These viruses can cause severe disease and high mortality rates in infected birds[7]. The second group comprises low pathogenic avian influenza viruses (LPAI), which include all other subtypes of HA and NA. LPAI viruses generally cause milder or asymptomatic infections in birds and have a lower risk of severe disease or death.

Phylogenetic studies of influenza A viruses have provided insights into the evolutionary relationships between viral genes and highlighted the existence of distinct lineages unique to specific animal species. These studies show that the occurrence of interspecific transmission varies depending on the species of animal involved .They also disclosed that wild aquatic birds are a large and antigenically diverse reservoir of influenza A viruses, in which the infection is usually asymptomatic [8].

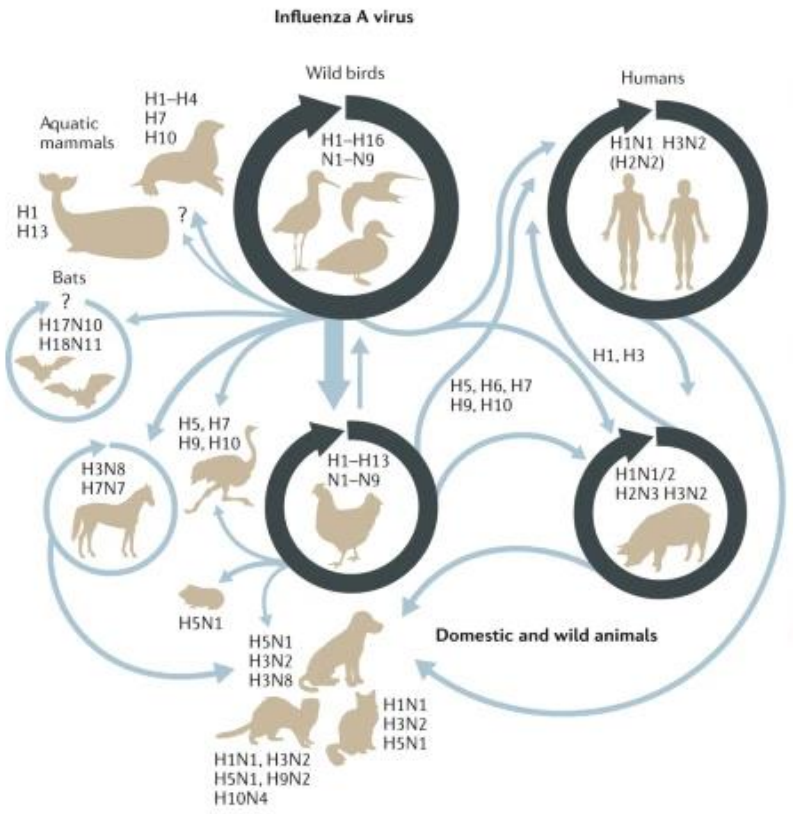

Figure 2 : Ecology of influenza viruses

As the table 1 show there are various types of influenza A viruses, all of them exist in birds, and H9N2 is among them.

H9N2 influenza viruses were first isolated from turkeys in North America in 1966[9]; since then the virus has experienced extensive spread within poultry populations across various countries worldwide. Following its introduction to Africa in 2011, notably in Egypt, the virus subsequently spread to Morocco and Tunisia in 2016. Since then, it has continued its expansion into West Africa, affecting multiple countries in the region since 2017[10].

2. H9N2 virus characteristics

2.1. Classification

H9N2 is classified as a low pathogenicity virus, studies have shown that certain respiratory microbial agents and environmental factors may exacerbate IAV H9N2 infection and lead to very severe respiratory disease and causing mortality up to 65 % in broiler chickens and up to 70 % drop in egg production in layers and breeders [11]

2.2. Molecular structure

The HA gene of H9N2 viruses can be divided into two main branches: a Eurasian branch and an American branch[12].The American H9N2 virus is predominantly found in wild birds, but has been observed to infect farm turkeys, but does not spread stably in bird populations. In contrast, the Eurasian H9N2 virus has established at least three stable lineages in poultry, named after its prototype virus and they have distinct structural differences.

- *Lineage G1*: This lineage is related to the prototype virus A/quail/Hong Kong/G1/1997. It can be divided into two phylogenetic and geographical sublineages, termed the "Western" and "Eastern" sublineages.
- *Lineage BJ94 (also known as lineage Y280 or G9*): This lineage is related to the prototype virus A/chicken/Beijing/1/94. It is also common in Eurasia, where it is found in several countries. It is sometimes referred to as the Y280 lineage, in reference to the prototype A/chicken/Hong Kong/Y280/1997 virus.
- *Lineage Y439 (also sometimes known as the Korean lineage*): This lineage is associated with the prototype virus A/chicken/Hong Kong/Y439/1997. It is present in Eurasia, notably in Korea.

Since the project focuses specifically on chickens in Morocco, a study carried out by researchers from the first introduction and isolation of the virus found that the H9N2 viruses belong to the G1 lineage and probably originate in the Middle East. It is essential to understand the molecular structure of H9N2 viruses isolated in Morocco to assess its pandemic potential and implementing appropriate control measures.

Extensive molecular characterization of Moroccan H9N2 isolates revealed several important determinants. In HA, the HA0 cleavage site displays the RSSR*GLF motif characteristic of low pathogenic avian influenza virus, and the HA protein is glycosylated at seven potential sites. In NA, no mammalian adaptation-related substitutions or stalk deletions were observed. The virus's internal genes also display mammalian adaptation markers in the PB2, PB1, and PA proteins, and specific substitutions in NP, M2, and

NS1(table2). These molecular features provide clues to understand the virulence and host specificity of the Moroccan H9N2 isolate.

Protein	Molecular determinants of virulence	Molecular determinants of host specificity (adaptation to mammals)
PB2	147 V, 504 V	318R, 590S, 661 T
PB1		13P
PB1-F2	66 N	82 L
PA	127 V, L550, 672 L	I100, R312, 409 N
PA-X		
HA[a]		158 N, 183H, 226 L, 391 K
NP		372D
NA		
M1		15I
M2		D16
NS1	42S, 189D	
NS2	31 M, 56H	

Table 2 : Molecular determinants of virulence and host specificity

2.3. Phylogeny:

Phylogeny plays a crucial role in the study of viruses, helping us to understand their evolution and genetic diversity. It enables us to reconstruct kinship links between viral strains, identify new emerging strains and detect virulence and interspecies transmission factors. By tracking the evolution of viruses, phylogeny helps us to predict the emergence of new strains and adapt prevention and control strategies accordingly.

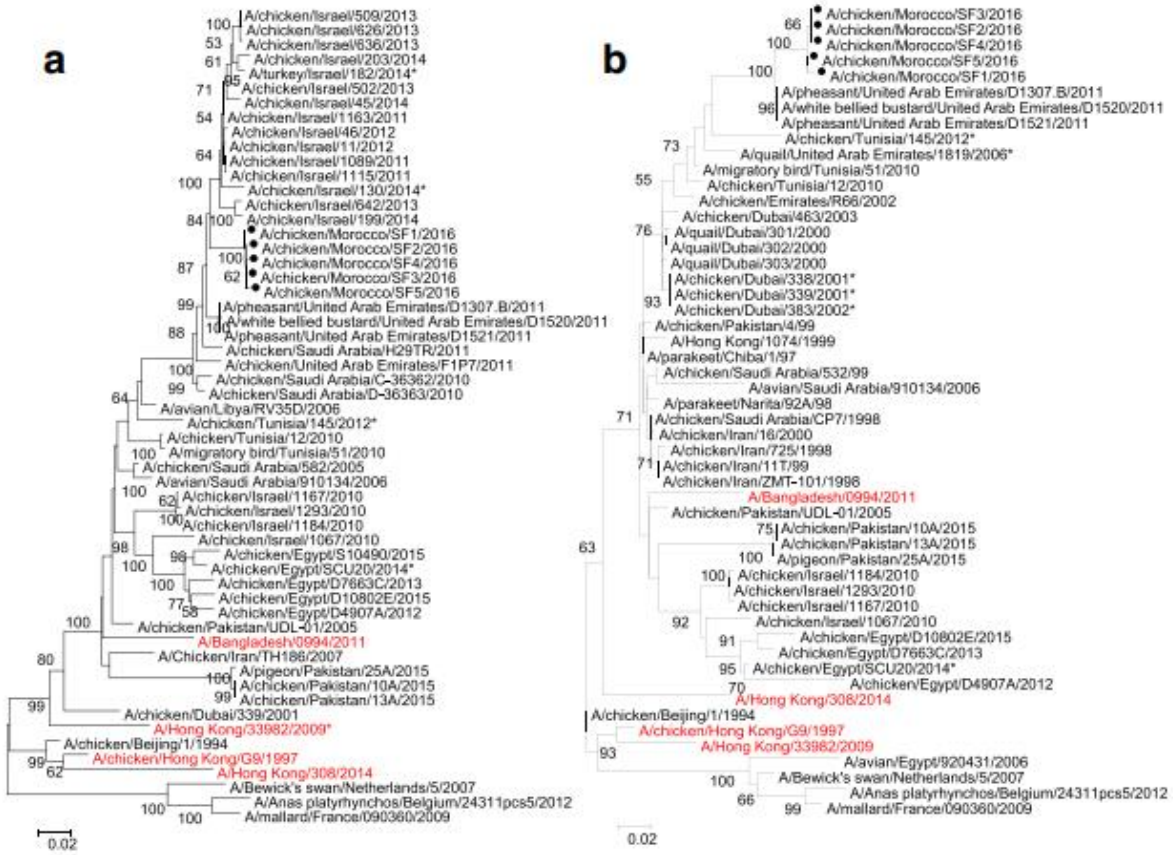

Figure 3 : Phylogenetic analysis of Moroccan HA and NA gene segments

The Moroccan H9N2 viruses exhibited a tight association with viruses from the Middle Eastern G1 lineage based on the phylogenetic analysis of the HA and NA genes(figure3). The Moroccan viruses are most likely the ancestors of the Middle Eastern strains due to the genetic similarities between our viruses and those from Israel and the United Arab Emirates. The HA protein's extra glycosylation sites and particular mutations suggest viral adaptability and possible human transmission. These results underline the significance of thorough genome sequencing to comprehend the genesis and spread of H9N2 viruses in Morocco.

3. H9N2 epidemiology

The H9N2 virus is highly contagious, with wild birds serving as natural reservoirs of the virus. It can spread through various means, including contaminated dust, water, food, clothing, shoes, and farm equipment. The H9N2 virus is widespread throughout the world, with significant prevalence in Asia, the Middle East and North Africa (figure4). It has been detected in many countries in these regions, and its geographical distribution continues to expand. The spread of the virus is influenced by several factors, such as avian population density, commercial poultry movements, international trade and wild bird migrations. These factors favor transmission of the virus between chickens and other avian species, contributing to its spread. The prevalence of the H9N2 virus in these regions underscores the need for surveillance and control measures to limit its spread and prevent negative consequences for poultry populations.

Figure 4 : Phylogeographic range of poultry-adapted H9N2 lineages

4. Health and economic impacts

Infection with the H9N2 virus has a significant impact on chicken health, manifesting itself in various clinical symptoms such as labored breathing, reduced appetite, lower egg production and quality, as well as respiratory problems and lung lesions. Morbidity, i.e. the number of infected animals, can be high, while mortality varies according to factors such as virus strain, rearing conditions and the presence of other diseases.

In economic terms, widespread infection with the H9N2 virus is having a considerable impact on the poultry industry. Production losses are observed due to reduced chicken growth, reduced egg production and increased mortality. Treatment costs, including drugs and biosecurity measures, are rising to control the spread of infection. In addition, trade restrictions lead to reduced exports of poultry products, loss of income for poultry farmers and financial difficulties for poultry companies.

5. Prevention and control measures

Prevention and control measures play a crucial role in limiting the spread of the H9N2 virus. Currently, several strategies are being implemented to prevent infection and reduce transmission. Among these strategies is the implementation of rigorous biosecurity practices on poultry farms. This includes measures such as strict control of animal movements, regular disinfection of facilities, limiting access of unauthorized persons to poultry areas, and the use of appropriate protective clothing and equipment.

Vaccination is also widely used as a means of controlling the H9N2 virus. Targeted vaccination programs are implemented to immunize poultry against the virus, thereby reducing the prevalence of infection in poultry populations. Vaccination can be carried out using several types of vaccines such as:

- **Inactivated vaccines**: contain killed or inactivated viral particles that cannot cause infection
- **Live attenuated vaccines**: use a weakened (or attenuated) form of the germ that causes a disease. Because these vaccines are so similar to the natural infection that they help prevent, they create a strong and long-lasting immune response.
- **Vectorized vaccine**: contain a weakened version of a virus that is harmless to humans, into which some of the virus's genetic material has been introduced. When the viral vector enters our cells, it gives instructions to make the S protein.

That are administered according to a specific schedule based on needs and health authority recommendations.

In addition to biosecurity and vaccination measures, other prevention and control measures are also used to limit the spread of the H9N2 virus. These include regular surveillance of poultry flocks to detect any presence of the virus early and take appropriate action. Screening and diagnostic programs are put in place to identify outbreaks and take measures to quarantine and eliminate infected animals.

6. Conclusion

Raising awareness and educating poultry farmers and workers also play a crucial role in preventing H9N2 infection. Information campaigns are carried out to inform people about the risks associated with the virus, the preventive measures to be taken and the clinical signs to watch out for. This contributes to a better understanding of the disease and wider adoption of recommended biosecurity practices.

Chapter 3: Literature Review

In this chapter, we have expanded our analysis to include studies on determining the optimal age for vaccination against contagious respiratory illnesses, such as influenza, using mathematical modeling. We examine different approaches and models used to assess the effectiveness of vaccination at various ages, considering factors that influence this effectiveness. For each method we represent some examples of the articles that treat it.

1- Introduction

Mathematical modeling plays a vital role in the field of vaccination, providing precise and rigorous methods for assessing the effectiveness of vaccines and predicting their impact on the spread of infectious diseases. With the help of mathematical models, different vaccination scenarios can be analyzed, the effectiveness of vaccination programs can be assessed, and recommendations can be made to optimize vaccination strategies.

These models can be used to simulate disease transmission in populations, taking into account parameters such as vaccination coverage, duration of immune protection, natural immunity, and disease transmission dynamics. Thanks to these simulations, it is possible to estimate the short- and long-term effects of vaccines, predict the effectiveness of different vaccination strategies, and identify target populations that will be most beneficial in reducing disease transmission.

Mathematical modeling can also predict the emergence of new virus strains and estimate the impact of vaccination on their spread. This information is critical for making informed public health policy decisions by adjusting immunization programs, targeting the most vulnerable and optimizing the allocation of available resources.

2- Search methodology

To conduct a comprehensive literature search, we employed a systematic approach known as a systematic literature review[13]. Our search aimed to gather relevant studies on the determination of the optimal age for vaccination against contagious respiratory illnesses, such as influenza, using mathematical modeling. We utilized the search strings "contagious respiratory illnesses" AND "mathematical modeling" as well as "contagious respiratory illnesses" AND "mathematical models" combined with "vaccine strategy" to identify articles pertaining to our research topic. These search queries were employed while searching scientific databases such as PubMed, ScienceDirect, and NCBI. The search was conducted within the timeframe of 2020 to 2022, ensuring the inclusion of recent publications.

By following this methodology, we obtained a total of 1,123 articles. These articles underwent a selection process where duplicate articles were removed, resulting in 905 unique articles. Subsequently, the articles were screened based on their titles and abstracts,

leading to the exclusion of 154 articles. Finally, a thorough evaluation of the remaining articles' full texts was performed, resulting in the inclusion of 54 articles that aligned with the scope and treat different methods.

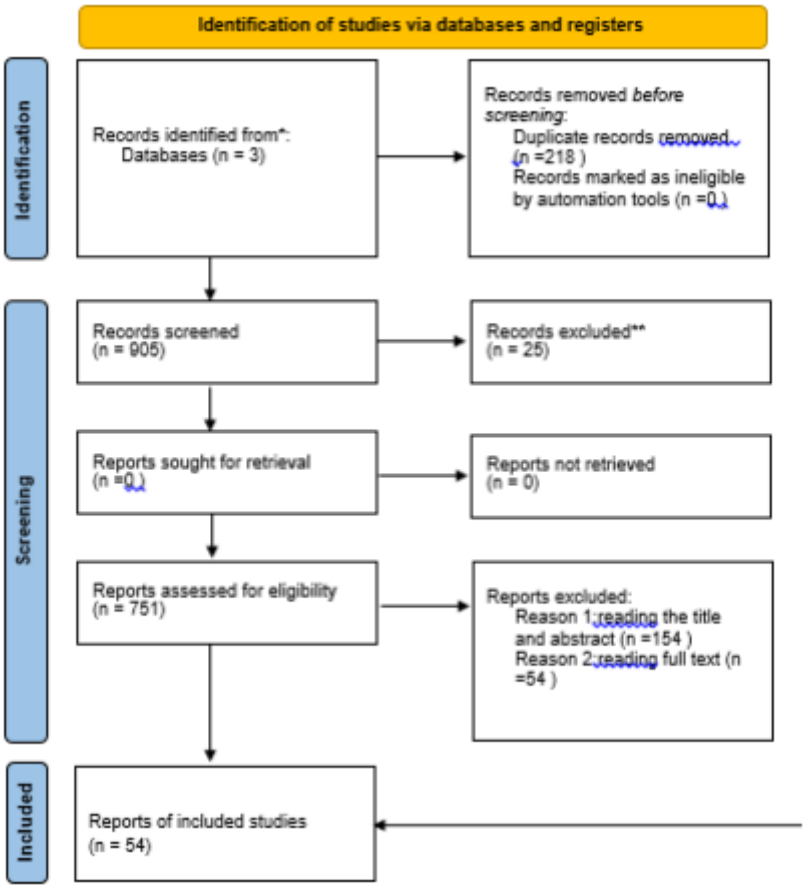

Figure 5 : Research Strategies and Research Methods

Of the 54 articles studied, a careful analysis revealed that 3 focused on the Kouwenhoven formula. In addition, 6 articles were devoted to the Deventer formula a well-known method. In addition, a majority of 28 papers dealt with deterministic models, highlighting their popularity and relevance. As far as stochastic models, 12 were dedicated. Finally, 12 articles were dedicated to hybrid models are concerned, five articles were identified, testifying to the interest in this approach which combines determinist and stochastic models.

3- Deterministic models

Deterministic models play a crucial role in understanding and predicting the spread of infectious diseases. These mathematical models are used to analyze, evaluate, and implement effective control programs. In the context of epidemiology, deterministic compartmental modeling is widely employed. In deterministic compartmental modeling, the population is divided into compartments or classes, representing different stages of the epidemic. The most commonly used model is the susceptible-infected-recovered (SIR) model that was introduced by Kermack and McKendrick in 1927.[14]

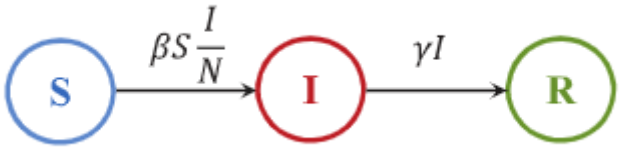

Figure 6 : Basic SIR model without vital dynamics

The SIR model was developed with time to adapt to different situations, a compartment or plus can be added or deleted. A variation of the SIR model known as the S model can be used to research vaccination[15]–[19]. To track the population that has undergone vaccination and may behave differently from the susceptible population, a compartment labeled "vaccinated" (V) is introduced to the model. This enables researchers to calculate parameters relating to vaccine effectiveness, coverage, and timing and study the effect of vaccination on the spread of illness. Similarly, the SIR model can be extended to incorporate the effects of MDA. An extra compartment, denoted as M, can be introduced. This would result in the MSVIR model, where individuals in the M compartment are characterized by altered dynamics due to the presence of MDA and the potential protection it offers against the disease.[20]. The predictive power of the model in assessing the effectiveness of different vaccination strategies can be improved by including different factors such as age group and vaccination status[21], [22], that was used in most of articles with different model[23], [24].

Deterministic models are formulated using differential equations, which describe the rates of change of the different compartments over time. The figure can be translated into the following set of differential equations:

$$\frac{dS}{dt} = -\beta S \frac{I}{N} \qquad (1)$$

$$\frac{dI}{dt} = \beta S \frac{I}{N} - \gamma I \qquad (2)$$

$$\frac{dR}{dt} = \gamma I \qquad (3)$$

Summing up (1), (2), and (3) yields zero which implies that the population is of constant size with $S + I + R = N$

By solving the system of differential equations, researchers can obtain a mathematical representation of how the disease spreads through the population over time. This allows them to make predictions about the future course of the epidemic, assess the impact of different control measures, and evaluate the effectiveness of interventions.

The epidemiological threshold R_o is a key parameter that determines whether an epidemic will spread or die out. When R_o is less than 1, each infected person will transmit the disease to less than one other person, leading to a decrease in the number of infections over time. In this case, the epidemic will gradually die out. On the other hand, when R_o is greater than 1, each infected person will transmit the disease to more than one person, leading to an increase in the number of infections over time. This indicates that the epidemic will spread. The R_o is a crucial measure in epidemiology as it allows us to assess the potential for a disease to spread. If R_o is less than 1, appropriate control and intervention measures may be sufficient to contain the epidemic. On the other hand, if R_o is greater than 1, more stringent measures are required to halt the spread of the disease.

Related works:

Among the models founded, the SVIR model stands out because it divides the population into susceptible (S), vaccinated (V), infected (I) and recovered (R) compartments. The articles deal with different aspects and variations of the SVIR model and emphasize its versatility and adaptability to different scenarios. A common thread among these articles is the use of the SVIR model to analyze the spread of COVID-19 and assess the effectiveness of different vaccination approaches. They use mathematical modeling techniques and simulated scenarios to study various factors affecting disease spread and control. Furthermore, they both considered the baseline reproduction number as the threshold for determining whether a disease would spread or become extinct in a population. Although they share a common focus on the SVIR model, each article explores different aspects and variations within this framework. For example Xinyu Liu and Yuting [25]emphasize the impact of time delays in the model, specifically related to booster vaccination and the duration of vaccine efficacy. The study investigates the stability of non-negative equilibrium and explores the occurrence of Hopf bifurcation as critical values of vaccine duration are crossed,while Herbert W.Hethcote and Paul Waltma [26]involves dividing the time horizon into discrete periods and determining the optimal vaccination strategy based on current epidemic conditions, achievable vaccination rates, and the cost of the vaccination program. Optimization problems are solved to minimize costs while controlling the epidemic. To solve the differential equations, Numerical integration techniques such as the Euler and Runge-Kutta[15].

There are some models that present an alternative to the SVIR model by introducing one additional compartment or more. For instance, the MSVIR model includes an extra compartment, denoted as M, representing the passive immunity transferred from mother to child during pregnancy and early infancy. This addition aims to capture the dynamics of maternal antibodies in the spread of tetanus disease within a population[20]. Similarly; the SVIR model includes multiple compartments representing different stages and states of individuals in the population. For example, in another study, a nine-compartment mathematical model of the age structure was used to analyze the effects of individual

vaccines, combined vaccines, and treatments in reducing COVID-19 infection. The model takes into account the time delay of control variables and state variables. These compartments represent different stages and states of individuals in the population, such as susceptible, infected, dead, vaccinated, partially vaccinated, exposed, hospitalized, not effectively vaccinated, and recovered individuals. To determine the optimal policy, both studies formulated the optimal control problem. Their goal is to minimize cumulative infection and disease-related mortality by identifying optimal vaccination and treatment rates[23].

There are models which do not necessarily include a V compartment to represent the vaccinated population. Instead, they incorporate the effects of vaccination through other systems inside the already-existing compartments. The SIQRD Model is one of the examples that does the same thing by segmenting the population into groups depending on health status, including susceptible (S), infected (I), quarantined (Q), recovered (R), and died (D). This study examines the distribution of COVID-19 in particular provinces using age-structured and non-age-structured SIQRD models.

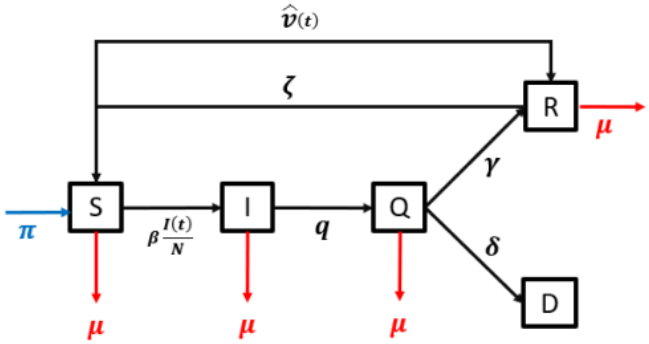

Figure 7: SIQRD model

The non-age-structured model was used to calculate the disease's transmission rate. Real data on cases, deaths, and recoveries in each province are used to calibrate the model. Incorporating age-specific dynamics, the age-structured model takes into consideration the differences in susceptibility, transmission, and recovery rates between age groups. The study examines how vaccination affects disease transmission by simulating the movement of individuals from compartments that are susceptible to the disease to compartments that have recovered. The percentage of people likely to recover or develop immunity following vaccination is evaluated to determine the effectiveness of the immunization. The study suggests an ideal immunization schedule using simulations, taking into account elements like cost, healthcare capacity, and daily vaccination capacity. The outcomes emphasize the value of timing and giving particular age groups priority in order to reduce casualties[21].

After presenting the deterministic models, it is important to highlight their limitations. These models often ignore parameter uncertainty, stochastic fluctuations in individual interactions,

individual behavior and rare events. To overcome these limitations, stochastic models are used.

4- Stochastic models

In the field of epidemiology, stochastic epidemic models offer a comprehensive and enhanced perspective compared to their simpler deterministic counterparts. These models are constructed using stochastic processes, which involve sets of random variables. By employing this approach, the solution of a stochastic model yields probability distributions for each random variable, enabling a deeper understanding of the dynamics at play.

One of the notable advantages of stochastic models is their ability to capture the inherent variability stemming from demographic and environmental factors. This variability is crucial to comprehending the complexities of real-world scenarios, especially when dealing with small population sizes. Moreover, stochastic models facilitate chance-based tracking of each individual within the population, allowing for a more realistic representation of how an epidemic unfolds[27].

Three types of stochastic modeling processes are described[28], [29]:

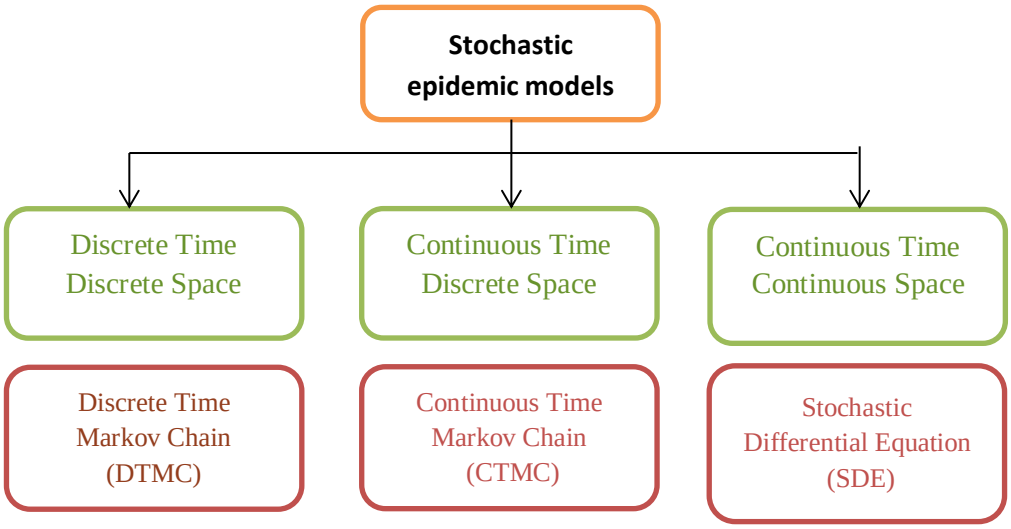

Figure 8: Classification of stochastic epidemic model

4.1. Continuous Time Markov Chain(CTMC)

Continuous-time Markov chain models (CTMC) are tools used in epidemiology to study the spread of infectious diseases. They allow the uncertainty and randomness of the transmission process to be taken into account, providing a realistic representation of the dynamics of epidemics. CTMC models are based on transitions between discrete states, which can occur at any time and are governed by the Markov property. Their mathematical analysis involves calculating transition rates, analyzing the stationary state and estimating key epidemiological parameters. These models provide invaluable information on the

prevalence and persistence of diseases and the assessment of the effectiveness of control measures[27].

The formulation of a continuous-time Markov chain model (CTMC) involves the following steps:

- **Define the state space**: Identify the different possible states of the system you wish to model. For example, in the context of an epidemic, the states could be "susceptible", "infected" and "cured".
- **Specify transition rates**: Determine the transition rates between the different states. These rates represent the probability per unit of time of moving from one state to another. They can be influenced by factors such as the infectiousness of the disease, contact rates between individuals and the effectiveness of interventions.
- **Write the stochastic differential equations**: From the transition rates, you can write the stochastic differential equations that describe the evolution of the system over time. These equations describe how the occupancy probabilities of the different states change over time.
- **Analyze the model**: Use mathematical techniques to analyze the CTMC model. This can include calculating steady state probabilities, estimating key epidemiological parameters such as the basic reproduction number, and assessing the sensitivity to different assumptions in the model.
- **Validate and adjust the model**: Compare the model results with real data to assess its validity and fit. If necessary, adjust the model parameters to better match the empirical observations.

4.2. Discrete Time Markov Chain (DTMC)

Discrete-time Markov chain (DTMC) model for stochastic epidemic modeling is a mathematical model that describes the evolution of an epidemic over discrete time steps. It assumes that the system can be in a finite number of states, and transitions between states occur at fixed time intervals. The transition probabilities between states are constant over time and depend only on the current state. DTMC models are computationally efficient and easier to analyze compared to continuous-time models. DTMC models are not flexible and can't capture more complex dynamics compared to DTMC models[27].

4.3. Stochastic Differential Equation (SDE)

A Stochastic Differential Equation (SDE) is a mathematical equation that combines deterministic and stochastic (random) elements to describe how a system changes over time. It is made up of a differential equation with added stochastic components that show how random fluctuations affect the behavior of the system[30].

Related works

The articles selected provide an overview of stochastic epidemic models, highlighting both the similarities and differences between them. The acknowledgement of the significance of taking elements like vaccination, variable parameters, and seasonality into account when modeling epidemics is a key theme running across the articles. As a result, it is feasible to get more accurate data and evaluate the success of prevention initiatives.

The study[31] examines a discrete-time Markov chain model with four states: vulnerable, immunized, infected, and recovered. This model provides a reliable method for forecasting the number of confirmed cases during the subsequent time period while accounting for vaccination and acquired immunity. It should be emphasized that the Markov chain's discrete structure might make it less able to accurately depict continuous transitions between states, which might limit the accuracy of forecasts in some circumstances.

The second study [32] presents an extended SEIR model that uses a continuous Markov chain to represent transitions between different classes of individuals over time. This approach enables more fluid and accurate modeling of disease spread, taking into account time delays and random noise. Theoretical results and numerical simulations reinforce the validity of the model for understanding disease behavior in real-life situations.

Another study [33]a stochastic SVIR epidemic model with age of vaccination and generalized nonlinear incidence. The transmission coefficient between the susceptible and the infected is described by a stochastic process instead of a constant. The authors use the generalized **Itô's** formula to derive the stochastic differential equation (SDE) for the model. They then establish sufficient conditions for extinction, weak permanence, and persistence in the mean of the infected population using Lyapunov function.

In conclusion, stochastic models have some drawbacks while being a powerful tool for modeling epidemics while accounting for uncertainty and variability. Their applicability in some circumstances may be constrained by their computational complexity, data needs, and interpretation of results, parameter sensitivity and limited generalizability. Hybrid models, however, offer a possible solution to these issues and provide a more accurate depiction of the complexity of epidemics.

5- Hybrid models

A hybrid model combines deterministic components, which use mathematical equations to describe the average behavior of the system, with stochastic components, which introduce randomness or uncertainty into the model. This combination allows for a more comprehensive representation of the real-world dynamic.

Related works

Hybrid models offer the flexibility to incorporate different compartments tailored to specific situations. The study [34]presents a mathematical model that simulates the spread of SARS-CoV-2 in the UK and evaluates the impact of different vaccination strategies. The model incorporates both deterministic and stochastic modeling approaches to account for the randomness and uncertainty associated with the spread of the virus and the effectiveness of vaccination strategies. The model divides the population into different compartments, including susceptible, exposed, infectious, hospitalized, ICU, recovered, and dead. It takes into account various factors such as age-specific contact patterns, disease transmission rates, and vaccine efficacy.

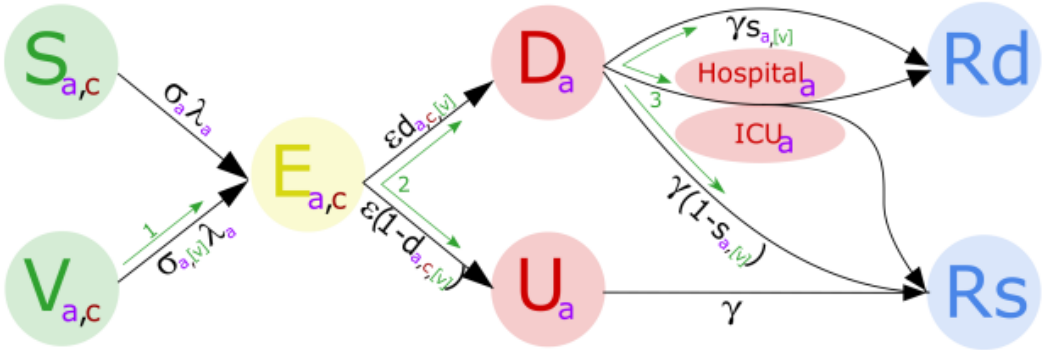

Figure 9: Representation of model states and transitions

The use of a stochastic modeling approach allows for the incorporation of random variation in model parameters and initial conditions, capturing the inherent randomness and uncertainty in the spread of the virus and the effectiveness of vaccination strategies.The study concludes that targeting older age groups first is the most effective way to minimize future deaths or quality adjusted life year (QALY) losses. The authors suggest that their findings may be applicable to other countries with similar age profiles and age-structured mixing patterns[34].

While the other study [35] the dynamics of the SLIARS model with demography, focusing on the impact of vaccination with imperfect and waning protection. The model incorporates compartments for susceptible (S), latent (L), infectious (I), asymptomatic (A), recovered (R), disease-induced death (D), and vaccinated individuals.By considering these compartments, the study explores the effects of vaccination on the spread of the disease and the overall dynamics of the system. The analysis combines deterministic and stochastic approaches, utilizing ordinary differential equation (ODE) and continuous time Markov chain (CTMC) models. The study also examines factors such as imperfect and waning vaccine protection, as well as the presence of bistability and backward bifurcation in the system. The findings contribute to understanding the effectiveness of vaccination strategies in controlling the spread of the disease.

These models can also be more difficult to apply and call more modeling knowledge. For academics and practitioners without a solid foundation in modeling and simulation, the related mathematical equations, stochastic processes, and computational techniques may be difficult to understand.

6- Kouwenhoven formula

The Kouwenhoven formula, described in 1992[36], aims to estimate the optimal age for vaccination against Gumboro disease of standard chickens based on a modeling maternal antibody decline over time.

$$\boldsymbol{X = \frac{\sqrt{A} - \sqrt{350\ or\ 500}}{k}}$$

With:

- **X** : optimal age for vaccination
- **A** : average maternal antibody titre at 1 day of age
- **350**: reference for "intermediate" vaccines
- **500** : reference for "hot" vaccines
- **k** : daily antibody decay rate

Before applying the Kouwenhoven, it is necessary to calculate the rate of decay of maternal antibodies. By plotting these measurements of antibody concentration against time since hatching, the logarithmic degradation curve can be observed, which means that the antibody concentration decreases rapidly at the beginning and then more slowly over time. Then, we fit the experimental data to a linear regression, we can obtain an equation that represents antibody decay over time and from his one the daily antibody decay rate is determined.

The predicted age at which antibody levels will have dropped enough for vaccination to offer reliable protection against the targeted disease is represented by the calculated vaccination age.

<u>Related work</u> : ” Determination de la date de vaccination contre la maladie de GUMBORO en elevage de poulets”

The article specifically focuses on the determination of the vaccination date against the disease of Gumboro (Infectious Bursal Disease) in label rouge chicken farming. The study aimed to develop a mathematical model to calculate the optimal vaccination date based on the level of maternal antibodies in chicks at birth and their decrease over time. The article mentions that the vaccination protocol applied in the study was successful in preventing clinical or subclinical signs of Gumboro disease, as evidenced by seroconversion in all the chicken groups tested. Additionally, when comparing the results to vaccination dates determined using databases provided by two laboratories, the study's method led to

proposing earlier vaccination dates when antibody titers were between 5000 and 6000 at 1 day of age. Therefore, the study provides valuable insights into determining the optimal vaccination date against Gumboro disease in label rouge chicken farming[37].

7- Deventer formula

The Deventer formula was developed by the Animal Health Service and has been used in the Netherlands since 1990.The MDA declines with time so we need to reach a sufficiently low level to allow vaccination[38].

Vaccination age = {(log2 titer bird% - log2 breakthrough) x t _ } + age at sampling + correction

In which:

- **Bird%** :ELISA titer of the bird representing a certain percentage of the flock
- **breakthrough** : breakthrough (ELISA) titer of the vaccine to be used
- **t _** : half-life time (ELISA) of the antibodies in the type of chickens being sampled
- **Age sampling** : age of the birds at sampling
- **Correction 0-4** : extra days when the sampling was done at 0 to 4 days of age

As the formula shows it is based on the level of maternal antibodies (MDA) as a function of sampling age, and on the specification of the percentage of the population likely to be vaccinated with titers equal to or lower than the Breakthrough titer. The half-life, also taken into account in the formula, represents the time required for antibody levels to fall by half. This means that after one half-life, around 50% of the antibodies initially present will have disappeared.

Using this information, the formula calculates the logarithmic difference between the antibody titer of a representative sample of the population (Bird%) and the Breakthrough titer. This difference is multiplied by the half-life (t _) to estimate the extent of antibody depletion. This value is then added to the initial sampling age and corrected if sampling took place between 0 and 4 days.

In this way, the Deventer formula integrates maternal antibody levels, breakthrough, half-life and sampling age to determine the optimal age for vaccination of chicks. This allows us to find the point at which antibody levels have fallen sufficiently for vaccination to confer lasting protection against the target disease.

The correction depends on the age of sampling as the table shows:

Age of sampling	Extra waiting days
0	4
1	3
2	2
3	1
4 or older	0

Figure 10: Number of extra days before vaccination according to the age of sampling

This updated formula is now the preferred method for estimating the optimal time for Gumboro vaccination in poultry flocks. Its flexibility allows for adjustments to different field situations, accommodating various types of chickens, age of sampling, percentage of flock, and different active vaccines.

Related work: "Estimation of Age of Infectious Bursal Disease Vaccination in Broiler Chickens in Haryana, India"

The study described in this article aims to determine the optimal age of vaccination for infectious bursal disease (IBD) in broiler chickens using the Deventer formula. The researchers collected serum samples from different hatcheries and calculated the maternal antibody (MAb) titers. They found a wide range of MAb titers, indicating significant variation among the hatcheries. Based on the calculated values, the researchers recommend vaccinating the chickens twice, with the first vaccination at around 9 days and the booster vaccination at around 16 days. However, further studies are needed to validate these findings[36].

8- Comparison

To facilitate a systematic understanding and comparison of the different approaches, we present a table that highlights the key characteristics of each method, allowing for a comprehensive evaluation and selection of the most suitable modeling technics:

Method	Description	Advantages	limitations	Required data	Vaccine type
Deterministic model	Deterministic models are based on mathematical equations that describe the disease spread and the effect	Predictability of results	Do not account for individual variability	Epidemiological data on virus or disease, vaccine effectiveness, transmission rates, demographic	All the types

	of vaccination.			data for each strategy of vaccination, etc.	
Stochastic Model	Stochastic models take into account random aspects of disease transmission, such as variability in individual contacts and environmental factors.	Can capture individual variability and uncertainties in predictions	may require a more in-depth statistical and computational ability than some of the more simple deterministic models	Epidemiological data on virus or disease, individual behaviors, demographic data for each strategy of vaccination, etc	All the types
Hybrid model.	Hybrid models combine elements of deterministic and stochastic models to capture both deterministic dynamics and stochastic variability of the disease.	Combine the advantages of deterministic and stochastic models	Can be more complex to implement and require expertise in modeling	Combination required data of deterministic model and stochastic one	All the types
Kounhouven	The Kounhouven formula is a specific mathematical formula used for determining the optimal age of vaccination against Gumboro.	Estimate the optimal age for vaccination besed on measurement of maternal antibody titers	Not adapted for all types of flocks and only applicable to active vaccines	Measurement of maternal antibody titers in chicks at birth and their decrease over time and the breakthrough of the types of active vaccine	Active vaccine against Gumboro
Deventer formula	The Deventer formula is another mathematical formula	Highly flexible, accurate, and can estimate the optimal	Relies on accurate information about vaccine-specific break-	Measurement of maternal antibody titers in chicks at birth and their	All the types of Gumboro vaccine

	utilized for estimating the optimal age for Gumboro vaccination.	age for vaccination in flocks with both uniform and non-uniform titer distributions. It is also practical and easy to use	through titers, is limited to Gumboro vaccines, and depends on the accuracy of half-life time measurements of maternal antibodies	decrease over time and breakthrough

Table 3 : Comparative table of methods

9- Conclusion

In conclusion, the modeling methods reviewed do not appear to be suitable for our specific situation; since we don't have the required data to implement those models. Given that the only data available to us are variations in maternally derived antibodies to H9N2 with and without vaccination, traditional models that require broader epidemiological data, such as transmission rates and vaccine efficacy, may not be directly applicable. It is important to note that the limited availability of data can be a significant limitation for traditional modeling methods. For this reason, we need to carry out our own mathematical modeling that takes into account the available data.

Chapter 4: Mathematical modeling to predict of the optimal age for vaccination against H9N2

In this final chapter, we present our own personalized mathematical modeling approach to determining the optimal age for vaccination against the H9N2 virus.

1. Data description and preprocessing :

1.1. Datasets description :

Our datasets contain measurements of maternal antibodies in broiler chicks reared in isolation at the Avian Pathology Unit of Hassan II-Rabat Agronomic and Veterinary Institute (IAV). Maternal anti-H9N2 antibody titers of the both dataset were measured using the hemaggglutination inhibition assay (HIA) according to the procedure β (constant antigen and serum serially diluted) according to the OIE manual (OIE, 2019). The standard Moroccan strain H9N2 antigen was obtained from the Laboratory of the Pharmacy and Veterinary Inputs Division, as well as ELISA.

Two commercial ELISA kits were used to determine the titer of antibodies of maternal origin against the LPAI H9N2 virus: ID Screen® Influenza H9 Indirect for the detection of antibodies directed against the H9 haemagglutinin of the Influenza A virus, and ID Screen® Influenza A Nucleoprotein Indirect for the specific detection and assay of antibodies directed against the nucleoprotein of the Influenza A virus. These ELISA kits were run according to the manufacturer's recommended protocol using an automated microplate reader (ELx800, BIO-TEK Instruments Inc, Winooski, VT)[39].

1.1.1. Variation of Maternal anti-H9N2 antibody without vaccination:

The dataset contains measurements of maternally derived antibodies in 20 individuals. Blood samples were taken by both kits on day one (D1) and every 7 days thereafter until the individuals reached 42 days of age.

First of all this is the data that I received:

Jours		1	7	14	21	28	35	42
individu 1	FLUNPS	11 649	5 006	4 595	3 174	2 775	896	375
	FLUH9S	18 811	12 107	7 452	2 640	1 038	237	155
individu 2	FLUNPS	11 642	4 328	4 228	3 073	884	424	299
	FLUH9S	18 393	7 319	6 082	2 612	503	202	83
individu 3	FLUNPS	11 543	4 319	2 519	2 985	855	291	258
	FLUH9S	17 874	6 013	5 022	2 538	486	153	81
individu 4	FLUNPS	11 529	3 475	2 391	2 575	565	287	202
	FLUH9S	17 827	4 448	4 897	1 949	465	95	47
individu 5	FLUNPS	11 487	3 463	2 080	1 137	514	273	139
	FLUH9S	17 687	4 419	3 638	1 871	349	86	47
individu 6	FLUNPS	11 465	2 906	1 832	1 134	489	229	131
	FLUH9S	17 656	4 290	3 539	1 730	278	75	42
individu 7	FLUNPS	11 371	2 289	1 484	1 111	399	151	131
	FLUH9S	16 549	3 865	3 147	1 633	271	58	28

Figure 11: First data of Variation of Maternal anti-H9N2 antibody without vaccination

This data was not ready for pre-processing, for that I set up another one with the same inputs as shown in the figure 12:

individu	jour	MDA FLUNPS	MDA FLUH9S
individu 1	1	11 649	18 811
individu 1	7	5 006	12 107
individu 1	14	5 006	7 452
individu 1	21	3 174	2 640
individu 1	28	2 775	1 038
individu 1	35	896	237
individu 1	42	375	155
individu 2	1	11 642	18 393
individu 2	7	4 328	7 319
individu 2	14	4 228	6 082
individu 2	21	3 073	2 612
individu 2	28	884	503
individu 2	35	424	202
individu 2	42	299	83
individu 3	1	11 543	17 874
individu 3	7	4 319	6 013
individu 3	14	2 519	5 022
individu 3	21	2 985	2 538
individu 3	28	855	486
individu 3	35	291	153
individu 3	42	258	81
individu 4	1	11 529	17 827
individu 4	7	3 475	4 448

Figure 12: Data of Variation of Maternal anti-H9N2 antibody without vaccination

The data has 4 features with 140 rows:

- **Individu** : identifies each individual and is represented by a unique number, it has 20 modes individu1;….; individu20 .
- **Jour**: quantitative variable that represent the age of blood sampling contains the 7 days of age (1, 7, 14, 21 28, 35, 42) for each chick.
- **MDA FLUNPS**: MDA measured using FLUNPS kit for each individual on a given day. It is a quantitative variable of min 23 and max 11649.
- **MDA FLUH9S**: MDA measured using FLUH9S kit for each individual on a given day. It is a quantitative variable of min 1 and max 18811.

1.1.2. Variation of Maternal anti-H9N2 antibody with vaccination:

The second set of data concerns the variation in antibodies each week by trying vaccination at different times: at day 1, between 5 and 7 days, and finally at 14 days. Blood samples were taken on day 1 and every 7 days thereafter until individuals reached 35 days of age. Measurements were taken for each batch using both kits.

So the data that I received has 3 sheets; every sheet concern an age of vaccination.

LOT	Vaccin	1	7	14	21	28	35
		FLUNPS	FLUNPS	FLUNPS	FLUNPS	FLUNPS	FLUNPS
1	C	9355	5115	1378	312	878	1146
2	C	13910	12537	6723	909	335	596
3	C	7568	6697			797	951
4	C	7701	4840	1332	530	431	1269
5	C	9791	6683	2295	519	326	245
		FLUH9S	FLUH9S	FLUH9S	FLUH9S	FLUH9S	FLUH9S
			11106	6148	920	95	
			12534		774	399	
		14505	13908			190	555
		12235	7566	1418	322	149	
			11830	7344	2988	489	127

Figure 13:First vaccine data

The figure 13 shows there is some empty cells especially for FLUH9S kit, also some observations doesn't represent an immune response. Since we are interested on the immune response of the vaccination, I create a data that contains only the rows when an immune response is observed for FLUNPS kit (the number of MDA increase in taking account the age of vaccination plus the latency because we are working with an inactivated vaccine).

lot	jour_vaccin	jour	MDA
1	5j_7j	1	9355
1	5j_7j	7	5115
1	5j_7j	14	1378
1	5j_7j	21	312
1	5j_7j	28	878
1	5j_7j	35	1146
2	5j_7j	1	13910
2	5j_7j	7	12537
2	5j_7j	14	6723
2	5j_7j	21	909
2	5j_7j	28	335
2	5j_7j	35	596
3	5j_7j	1	9791
3	5j_7j	7	6683
3	5j_7j	14	2295
3	5j_7j	21	519
3	5j_7j	28	326
3	5j_7j	35	245
4	1	1	7772
4	1	7	3142
4	1	14	608
4	1	21	923
4	1	28	1114
4	1	35	870

Figure 14: Vaccine data

The new data contains 46 rows with 4 columns:

- **Lot**: identifies each batch and is represented by a unique number. Lots are identified as "lot 1", "lot 2", …, "lot7"
- **Jour_vacin** : the time of vaccination ,there's : 1 , 14 and 5j_7j, which means that the vaccination took place between 5 and 7 days.
- **MDA**: MDA measured using FLUNPS kit for each batch on a given day;
- **Jour**: represent the age of blood sampling contains the 6 days of age (1, 7, 14, 21 28, 35) for each batch. It is a quantitative variable of min 245 and max 13910

1.2. Datasets preprocessing:

1.2.1. Variation of Maternal anti-H9N2 antibody without vaccination:

The first step was to find the missing values and their percentages for each column. In our case, after running the query, we find that there are no missing values.

```
la dataframe selectionnée 4 colones 140 lignes.
il y a 0 colonne qui ont des valeurs manquantes.
   Zero Values  Missing Values  % of Total Values
```

Figure 15:Missing values results

After that we plot a graph showing the geometric mean titers of maternal anti-H9N2 antibodies at different ages by the two ELISA test kits.

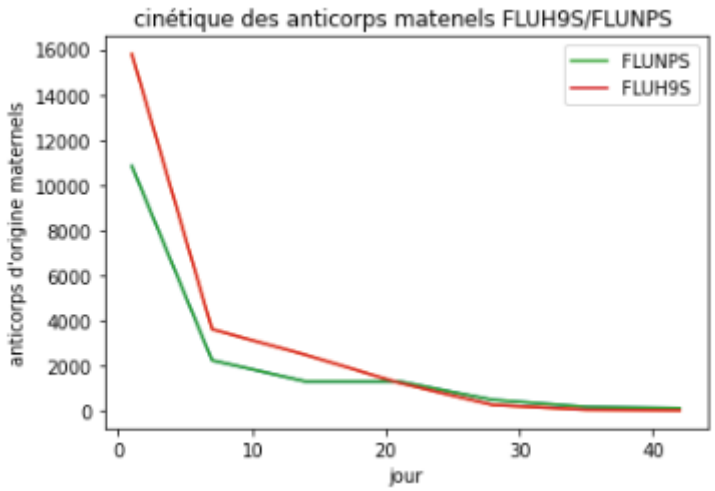

Figure 16: Maternal antibody cenitics FLUNPS/FLUH9S

Anti-H9N2 antibodies showed a progressive decrease in titer and was almost exhausted at D28.

1.2.2. Variation of Maternal anti-H9N2 antibody with vaccination:

In this dataset we found that there are no missing values. As mentioned before, we are interested here on the immunity response, for that we did an operation consists of replacing the values in the 'MDA' column with zero if the value in the 'jour' column is less than the sum of the value in the 'jour_vaccin' column and 14 ,because we will still have antibodies degradation. Otherwise, the value in the 'MDA' column remains unchanged.

	lot	jour_vaccin	jour	MDA
0	1	7	1	0
1	1	7	7	0
2	1	7	14	0
3	1	7	21	312
4	1	7	28	878
5	1	7	35	1146
6	2	7	1	0
7	2	7	7	0
8	2	7	14	0
9	2	7	21	909
10	2	7	28	335
11	2	7	35	596

Figure 17:Preprocessed data_vaccine

Then we plot the graph of the mean titer of maternal anti-H9N2 antibodies at different ages to represent the immunity response

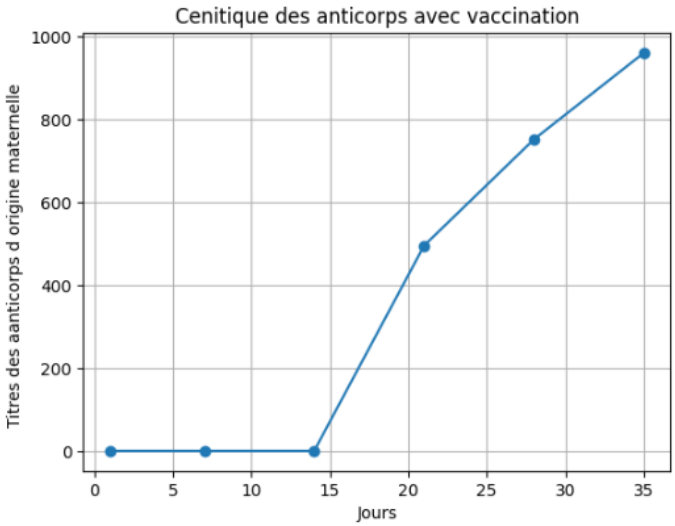

Figure 18: Graphical Representation of Mean Titers of Maternal Anti-H9N2 Antibodies at Different Ages: Immune Response Analysis

Anti-H9N2 antibodies showed a progressive increase in titer with time after the 14 day.

2. Mathematical modeling of the problem

2.1. Antibody degradation modeling

The figure 18 shows that the decrease of maternal antibodies follows a decreasing exponential curve. It can therefore be represented using the equation:

$$A(t) = A0 * e^{-kt} + C$$

With:

- **A(t)** : the level of maternal antibodies at a given time t
- **A0** : the initial level of maternal antibodies
- **k**: the degradation rate of maternal antibodies.
- **C**: constant

In fact, an adjustment must be made in order to determine the values of the parameters A0, k, and C of the above equation. The adjustment entails comparing experimental data or information provided with equation predictions, then estimating the parameter values that minimize the difference between the two.

The method of least squares, is frequently employed for curve adjustment. This method involves minimizing the sum of the squares of the differences between the observed values and the values predicted by the equation.

We obtain:

```
A_0 = 19235.811483978792 , k = 0.23817466954379318 , c = 553.838193677667
<ipython-input-59-0c7f894857f1>:6: RuntimeWarning:

overflow encountered in exp
```

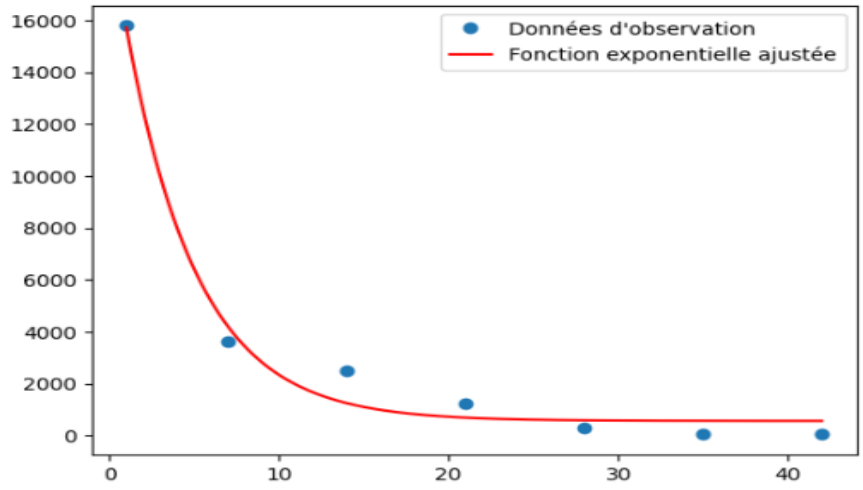

Figure 19: Adjustment for FLUH9S kit

For FLUH9S kit, k is 0.238, this would mean that 23.8% of the remaining maternal antibodies decompose per week.

```
A_0 = 13625.854108515605 , k = 0.28738947672854714 , c = 595.9708455273094
<ipython-input-11-4ba5bb19189c>:5: RuntimeWarning: overflow encountered in exp
  return a * np.exp(-b * x) + c
```

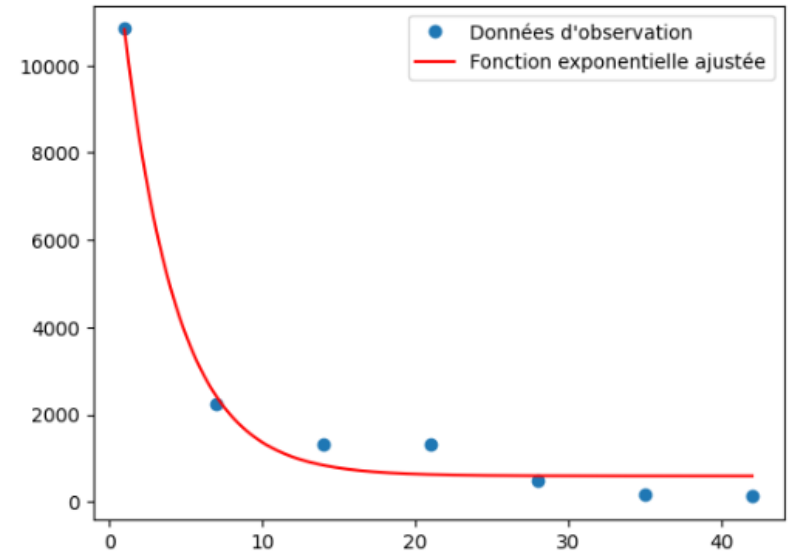

Figure 20:Adjustment for FLUNPS kit

For FLUNPS kit, k is 0.287 this mean that 28.7% of the remaining maternal antibodies decompose per week.

We check the quality of the fit by calculating the coefficient of determinationR^2, which indicates the proportion of variation in the data that is explained by the equation.

The R^2values obtained are 0.985 for FLUH9S and 0.987 for FLUNPS. It is high for both kits and close to 1, indicating that the equation is a good fit to the observed data.

2.2. Immune response modeling

The level of remaining maternal antibodies is a very important factor, which can affect the poultry to produce their own immune response to the vaccine. In some cases, the level of maternal antibodies may be high and may inhibit the immune response to the vaccine, while in other cases the level of maternal antibodies may be low response to the vaccine, while in other cases the maternal antibody level may be low and may allow a stronger immune response.

The figure shows that the increase of maternal antibodies follows a logarithmic curve. It can therefore be represented using the equation:

$$Y(t)= Y0 * \log (k1* t)+C1$$

With :

- **Y(t)**: the level of maternal antibodies at a given time t (the time elapsed since vaccination in days)
- **Y0**: the initial level of antibodies as soon as we start to see a response
- **k1**: the growth rate of antibodies
- **C1**: constant

The method of least squares is applied to make a fit and to determine the values of the parameters:

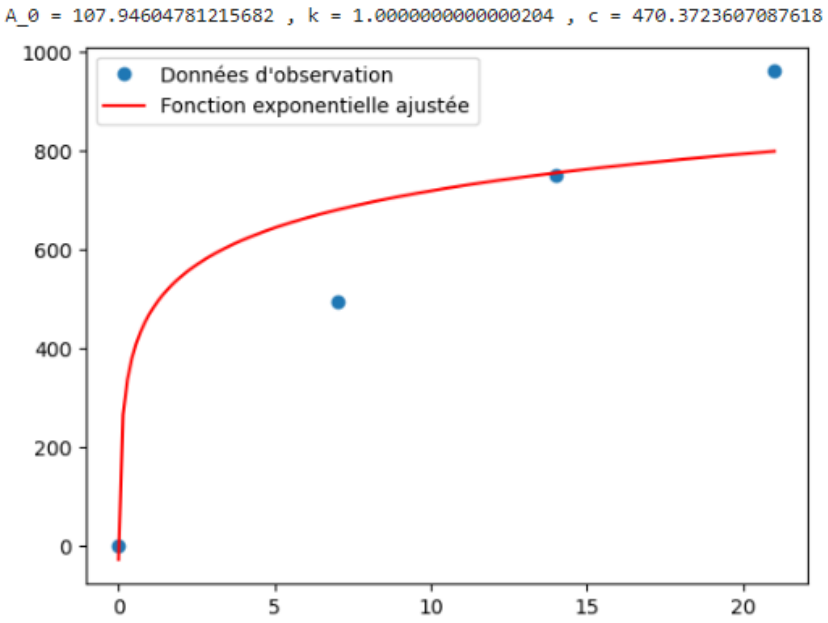

Figure 21:Adjustment for data vaccine

Note: this adjustment concern only the FLUNPS kit

After that the R^2 was calculated **.** The R^2value obtained is 0.881, it is high indicating that the equation is a good fit to the observed data.

2.3. Model 1:

This model will be based on the cut_off defined by a unit of activity in a serodiagnostic test which makes it possible to identify whether an animal is probably infected by a given pathogen by measuring the quantity of antibodies present in its blood. If antibody activity exceeds the threshold, the animal is considered positive, indicating a low probability of infection, while activity below the threshold classifies it as negative, indicating a high probability infection[40]. In our case, ELISA tests using the FLUH9S kit showed a cut-off of 732, while the FLUNPS kit showed a cut-off of 668.

The goal of this model is to find the age where all the chicks arrive to the cut-off so we can apply the vaccination.

Based on the equation of antibody degradation, we determine the equation of the time required:

$$t = -\frac{1}{k} * log\left(\frac{cut_{off} - C}{A0}\right)$$

with :

- **k** : the degradation rate of maternal antibodies
- **Cut_off** : The threshold of the ELISA kit
- **A0** : the number of antibodies on the first day
- **C** : constant

2.4. Model 2

This second model will be an optimization problem, requiring the modeling of both antibody degradation and the immune response to be taken into account, it will be implemented only for FUNPS kit. Before we start, we need to talk about latency, which is very important in the study of an inactivated vaccine, and which represents the time needed before an immune response occurs, in our case estimated at 14 days.

❖ Antibody degradation modeling

The breakdown of antibodies will be influenced by the age of vaccination, since a latency period is required before the immune response develops. When we vaccinate at a certain age, we have to wait until the end of this latency period to observe the development of the immune response. However, during this period, antibodies can break down. So the age of vaccination plays a crucial role in the dynamics of antibody degradation and the immune response.

$$A(t, \text{age\_vaccine}) = \begin{cases} A0 * e^{-kt} + C & if \quad t \leq \text{age\_vaccine} + \text{latency} \\ 0 & if \quad t > \text{age\_vaccine} + \text{latency} \end{cases}$$

The parameters A_o, k and C are the same calculated by fitting the exponential function for the FLUNPS kit. (Figure 21 and 22)

❖ Immune response modeling

In this section, we will simulate the dynamics of the immune response, taking into account factors such as the age of vaccination and the latency period.

Note that z = age_vaccine +latency

$$Y(t, age\_vaccine) = \begin{cases} Y0 * log(k1 * (t - z)) + C1 & if \quad t > z \\ 0 & if \quad t \leq z \end{cases}$$

The parameters Y0, k1 and C1 are the same calculated by fitting the logarithmic function for the FLUNPS kit. (Figure23)

When modeling the immune response to the vaccine, the expression "t - z" is used to calculate the time elapsed since the end of the latent period. This allows the immune response to be taken into account only after the end of this crucial period, whereas before it, the immune response is considered to be zero.

❖ Objective function

This function represents the whole process of the degradation of maternal antibodies and the immune response to the vaccine. It combines these two components to estimate the total quantity of antibodies at a given age.

The first component, **A_residual,** corresponds to the quantity of maternal antibodies remaining at the age given. It is calculated using the function **A (age, age_vaccine),** which models the decrease in maternal antibodies over time.

$$A\_residual = A(age, age\_vaccine)$$

The second component, **Y_vaccine** represents the immune response to the vaccine. It is calculated using the function **Y (age, age_vaccine**), which models the growth of antibodies in response to vaccination.

$$Y\_vaccine = Y(age, age\_vaccine)$$

So the objective function:

$$Objective\ function(age, age\_vaccine) = A\_residual + Y\_vaccine$$

❖ Function f

A function **f (age_vaccine)** has been defined which plays a central role in the search for the optimal vaccination age. It uses the **objective_function** to calculate the total amount of antibodies at 35 days of age, taking into account both the degradation of maternal antibodies and the immune response to the vaccine. It should be noted that the age of 35 days was deliberately chosen to allow the observation of a significant immune response. Given that the maximum age of vaccination is 21 days, taking into account a latency of 14 days, the maximum age at which we can assess the immune response is 34 days. By choosing an age of 35 days, we ensure that we have enough days after the latency period to obtain a complete picture of the immune response.

By inverting the sign of the **function_objective** in the function **f(age_vaccine),** we transform the problem into a minimization problem, where we seek to find the vaccination age that

gives the smallest negative value, which corresponds to the largest total quantity of antibodies.

❖ **Constraints**

Two constraints were defined. The first constraint ensures that the vaccination age does not exceed 21 days. It is defined by the function constraint (age) = age - 21. This ensures that we take into account the practical limits of the vaccination age.

The second constraint, called constraint1, is a non-linear constraint that applies to the function f (age_vaccine). This constraint limits the value of f (age_vaccine) to not be less than a given value. After experimental tests we have chosen the value 500 as a limit value which means that the totality of the maternal antibodies must not be less than 500.

❖ **Optimal age**

The **age_optimal** function aims to determine the optimal vaccination age by maximizing the total amount of antibodies at 35 days of age, while respecting the defined constraints. It uses the minimize optimization method predefined to find the optimal value.

The bounds of the vaccination age are defined between 14 and 21 days, which correspond to the period during which vaccination can be carried out.

3. Materiels

In order to conduct the analysis and implement the proposed methodology, a specific set of tools and resources were utilized. This section provides an overview of the materials employed during the project. It includes details on the programming language, libraries, and optimization techniques that were utilized to carry out the curve fitting and optimization processes.

3.1. Programming Language

The implementation was carried out using the Python programming language, known for its versatility, extensive libraries, and suitability for data analysis and scientific computing.

3.2. Libraries Used

a) Pandas

The Pandas library was utilized for efficient data manipulation and analysis. It provides a powerful DataFrame structure to handle tabular data, facilitating various data operations such as filtering, grouping, and transformation.

b) Matplotlib

The Matplotlib library was employed for data visualization and plot generation. It offers a wide range of plotting functions and customization options to create clear and informative visual representations of the data.

c) NumPy

NumPy, a fundamental library for numerical computations in Python, was utilized for efficient handling of multi-dimensional arrays and mathematical operations. It provided the necessary tools for numerical computations and data manipulation.

d) SciPy

The SciPy library was used for its extensive collection of scientific computing functions. Specifically, the following functionalities were employed:

- ***scipy.optimize.curve_fit***: This function was employed for performing curve fitting using the least squares method. It facilitated finding the optimal parameters of a mathematical model that best fits the observed data.
- ***scipy.optimize.minimize***: The minimize function from SciPy was used to solve the optimization problem and determine the optimal value. It allowed for efficient iterative optimization by considering the specified constraints.
- ***scipy.optimize.NonlinearConstraint***: The NonlinearConstraint class from the scipy.optimize module was used to incorporate a nonlinear constraint into the optimization process. It provided the ability to impose additional conditions on the optimization problem.

e) scikit-learn (sklearn.metrics)

The scikit-learn library's sklearn.metrics submodule was employed to evaluate the performance of the fitted models. Specifically, the ***r2_score*** function was utilized to calculate the coefficient of determination R^2, which assesses the goodness of fit of the models to the observed data.

4. Results and discussion

Using the model based on the cutoff defined by each serological test kit, we find the following results:

	MDAFLUH9S_j1	ageMDAFLUH9S
0	18811	19.563393
1	18393	19.469044
2	17874	19.348867
3	17827	19.337813
4	17687	19.304710
5	17656	19.297344
6	16549	19.025485
7	16174	18.929250
8	16159	18.925355
9	16058	18.899030
10	15655	18.792315
11	15232	18.677307
12	15186	18.664608
13	15178	18.662396
14	15106	18.642432
15	14873	18.577166
16	14853	18.571517
17	12472	17.837955
18	12107	17.713247
19	11911	17.644720

Figure 22:model1 results for FLUH9S kit

For the FLUH9S kit, we observed that the chicks reached the cutoff of 732 at ages ranging from 19.563393 days for the first chick to 17.644720 days for the last chick. These results indicate that the chicks took on average around 1.92 days to develop sufficient antibody activity to be classified as positive according to the FLUH9S kit criteria.

	MDAFLUNS_j1	ageMDAFLUNPS
0	11649	17.696907
1	11642	17.694815
2	11543	17.665099
3	11529	17.660876
4	11487	17.648177
5	11465	17.641506
6	11371	17.612860
7	11339	17.603054
8	11191	17.557338
9	11141	17.541757
10	11026	17.505653
11	10882	17.459910
12	10796	17.432302
13	10789	17.430045
14	10721	17.408045
15	10396	17.300931
16	9719	17.066620
17	9657	17.044352
18	9603	17.024840
19	8778	16.712278

Figure 23:Model1 results for FLUH9S kit

On the other hand, for the FLUNPS kit, with a cutoff of 668, the chicks reached this threshold at different ages. The first chick reached the cutoff at 17.696907 days, while the last chick reached it at 16.712278 days. These results suggest that the chicks required on average approximately 0.98 days less to reach the level of antibody activity required to be considered positive according to the FLUNPS kit criteria compared to the FLUH9S kit.

In resume, the average number of days taken to reach the cutoff of 668 was approximately 17.44 days, with a maximum of 17.70 days. This indicates that most chicks reached the required level of antibody activity at the same time.

For the FLUH9S kit, the average number of days taken to reach the cutoff of 732 was approximately 18.79 days, with a maximum of 19.56 days. This suggests that the chicks generally took slightly longer to reach the required level of antibody activity compared to the FLUNPS kit.

This difference in time to cutoff can be attributed to a number of factors, including the composition and specific efficacy of the test kits, as well as individual variation in the immune response of the chicks.

The second model, which used a different approach, gave the result that 21 days is the optimal age for vaccination, with an antibody level of 596,554 units.

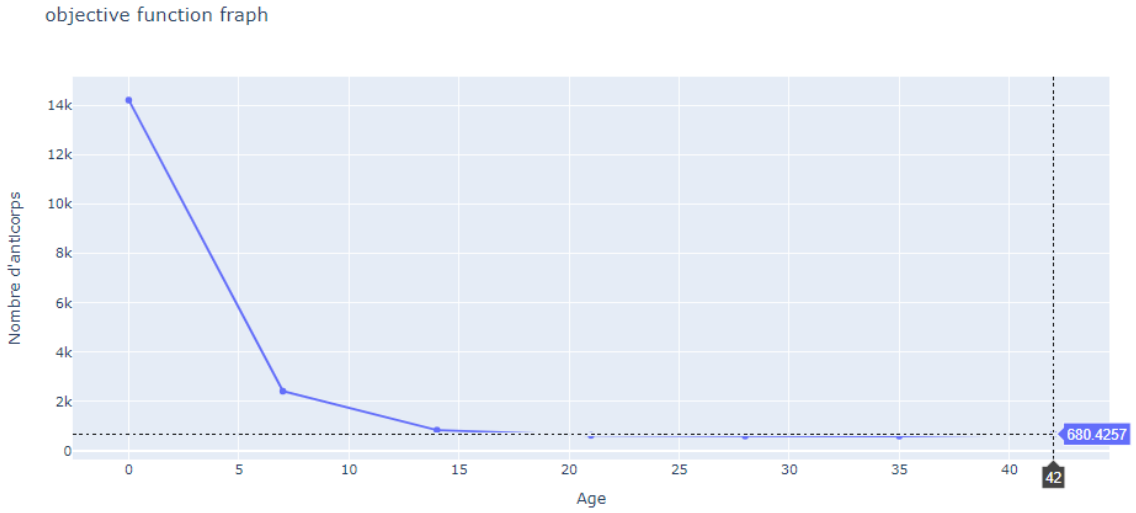

Figure 24: Variation of mean titers of maternal anti-H9N2 antibodies in response to vaccination at 21 days

As the plot shows if we vaccinate at 21 day after 14 days of latency we will star to have an immune response and if we take the example of 42 days we will have an antibody level of 680,42 units.

Comparing the two results for the FLUNPS kit, we can see that the first model recommended earlier vaccination (at a younger age) than the second model.

5. Limitations and recommendations:

In summary, our study has provided valuable insights into the optimal age for vaccination against H9N2. However, there are limitations to consider, such as variations between test kits and individual immune response factors. To overcome these limitations, future research should focus on evaluating different test kits, considering individual immune response, and exploring alternative modeling approaches. Additionally, expanding the dataset and collecting more comprehensive data will improve the accuracy of our findings. By addressing these limitations, we can refine our understanding of optimal vaccination strategies against H9N2 and enhance disease control measures.

Conclusion & perspectives

In conclusion, this project employed two mathematical models to determine the optimal age for H9N2 vaccination. The first model, based on antibody degradation and a cut-off point, indicated that most chicks reached the required antibody activity level in around 19 days, with a maximum of 20 days for the FLUH9S kit and 18 days, with a maximum of 18 days for the FLUNPS kit. The second model, an optimization problem considering both antibody degradation and the immune response, suggested that 21 days was the optimal age for vaccination, with an estimated antibody level of 596 units for the FLUNPS kit.

Our study highlights the importance of vaccination timing and its impact on the efficacy of protection against the H9N2 virus. By analyzing maternal anti-H9N2 antibody titers and employing mathematical modeling approaches, we gained valuable insights into the dynamics of the immune response. These findings emphasize the need for careful consideration of vaccination age in designing effective vaccination strategies.

Furthermore, our research extends beyond this study. We are developing a continuous-time Markov chain model to explore time-dependent transitions between different states, providing a more comprehensive analysis of optimal vaccination age. Additionally, we aim to enhance usability through a user-friendly graphical interface, facilitating data input, result visualization, and decision-making for healthcare professionals and policymakers.

Looking ahead, future research should expand the database and collect additional data, including demographic information, to gain a complete understanding of optimal vaccination age and enable comparisons between models. Exploring advanced modeling techniques will improve prediction accuracy and provide more robust recommendations for vaccination schedules.

Moreover, assessing the long-term efficacy of immune response at different ages is crucial. Evaluating the durability of H9N2 virus protection over time will help gauge the overall impact of vaccination strategies and their effectiveness.

In conclusion, while our study sheds light on the optimal age for H9N2 vaccination based on limited data, further research and data collection are needed to validate and refine our findings. By addressing the mentioned limitations and pursuing the outlined future research directions, we can advance vaccination strategies, enhance disease control measures, and safeguard public health.

Bibliography

[1] M. EL Houadfi, S. Fellahi, S. Nassik, J.-L. Guérin, et M. F. Ducatez, « First outbreaks and phylogenetic analyses of avian influenza H9N2 viruses isolated from poultry flocks in Morocco », *Virol. J.*, vol. 13, n° 1, p. 140, août 2016, doi: 10.1186/s12985-016-0596-1.

[2] R. G. Webster, W. J. Bean, O. T. Gorman, T. M. Chambers, et Y. Kawaoka, « Evolution and ecology of influenza A viruses », *MICROBIOL REV*, vol. 56, 1992.

[3] « Influenza (Avian and other zoonotic) ». https://www.who.int/news-room/fact-sheets/detail/influenza-(avian-and-other-zoonotic) (consulté le 24 juin 2023).

[4] « FluGlobalNet: About Avian Influenza ». https://science.vla.gov.uk/fluglobalnet/about_ai.html (consulté le 24 juin 2023).

[5] « L'influenza aviaire en 11 questions », *Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*, 9 février 2022. https://www.anses.fr/fr/content/linfluenza-aviaire-en-11-questions (consulté le 1 juin 2023).

[6] I. Kosik et J. W. Yewdell, « Influenza Hemagglutinin and Neuraminidase: Yin–Yang Proteins Coevolving to Thwart Immunity », *Viruses*, vol. 11, n° 4, p. 346, avr. 2019, doi: 10.3390/v11040346.

[7] A. R. Spickler, « Highly Pathogenic Avian Influenza ».

[8] J. S. Long, B. Mistry, S. M. Haslam, et W. S. Barclay, « Host and viral determinants of influenza A virus species specificity », *Nat. Rev. Microbiol.*, vol. 17, n° 2, Art. n° 2, févr. 2019, doi: 10.1038/s41579-018-0115-z.

[9] P. J. Homme et B. C. Easterday, « Avian Influenza Virus Infections. I. Characteristics of Influenza A/Turkey/Wisconsin/1966 Virus », *Avian Dis.*, vol. 14, n° 1, p. 66-74, 1970, doi: 10.2307/1588557.

[10] « Laprovet » INFLUENZA AVIAIRE FAIBLEMENT PATHOGENE H9N2 ». http://www.laprovet.com/wp/influenza-aviaire-faiblement-pathogene-h9n2/ (consulté le 1 juin 2023).

[11] « article_114_644d9318082618ac91713832886305e5.pdf ». Consulté le: 1 juin 2023. [En ligne]. Disponible sur: https://ijvr.shirazu.ac.ir/article_114_644d9318082618ac91713832886305e5.pdf

[12] T. P. Peacock, J. James, J. E. Sealy, et M. Iqbal, « A Global Perspective on H9N2 Avian Influenza Virus », *Viruses*, vol. 11, n° 7, p. 620, juill. 2019, doi: 10.3390/v11070620.

[13] W. Mengist, T. Soromessa, et G. Legese, « Method for conducting systematic literature review and meta-analysis for environmental science research », *MethodsX*, vol. 7, p. 100777, janv. 2020, doi: 10.1016/j.mex.2019.100777.

[14] A. Dadlani, R. Afolabi, H. Jung, K. Sohraby, et K. Kim, « Deterministic Models in Epidemiology: From Modeling to Implementation », *ArXiv Popul. Evol.*, avr. 2020, Consulté le: 21 juin 2023. [En ligne]. Disponible sur: https://www.semanticscholar.org/paper/0e08b7e385626b4c5857416de837cbf269ee2210

[15] Attaullah, A. Khurshaid, Zeeshan, S. Alyobi, M. F. Yassen, et D. Prathumwan, « Computational Framework of the SVIR Epidemic Model with a Non-Linear Saturation Incidence Rate », *Axioms*, vol. 11, n° 11, Art. n° 11, nov. 2022, doi: 10.3390/axioms11110651.

[16] Z. Lv, X. Liu, Y. Ding, Z. Lv, X. Liu, et Y. Ding, « Dynamic behavior analysis of an $ SVIR $ epidemic model with two time delays associated with the COVID-19 booster vaccination time », *Math. Biosci. Eng.*, vol. 20, n° 4, Art. n° mbe-20-04-261, 2023, doi: 10.3934/mbe.2023261.

[17] X. Liu, Y. Takeuchi, et S. Iwami, « SVIR epidemic models with vaccination strategies », *J. Theor. Biol.*, vol. 253, n° 1, p. 1-11, juill. 2008, doi: 10.1016/j.jtbi.2007.10.014.

[18] « Mathematics | Free Full-Text | Stability and Numerical Simulations of a New SVIR Model with Two Delays on COVID-19 Booster Vaccination ». https://www.mdpi.com/2227-7390/10/10/1772 (consulté le 24 juin 2023).
[19] C.-C. Zhu, J. Zhu, X.-L. Liu, C.-C. Zhu, J. Zhu, et X.-L. Liu, « Influence of spatial heterogeneous environment on long-term dynamics of a reaction-diffusion SVIR epidemic model with relaps », *Math. Biosci. Eng.*, vol. 16, nº 5, p. 5897-5922, 2019, doi: 10.3934/mbe.2019295.
[20] P. Widyaningsih, P. Candrawati, Sutanto, et D. R. S. Saputro, « Maternal Antibody Susceptible Vaccinated Infected Recovered (MSVIR) Model for Tetanus Disease and Its Applications in Indonesia », *J. Phys. Conf. Ser.*, vol. 1306, nº 1, p. 012002, août 2019, doi: 10.1088/1742-6596/1306/1/012002.
[21] G. González-Parra, M. R. Cogollo, et A. J. Arenas, « Mathematical Modeling to Study Optimal Allocation of Vaccines against COVID-19 Using an Age-Structured Population », *Axioms*, vol. 11, nº 3, Art. nº 3, mars 2022, doi: 10.3390/axioms11030109.
[22] G. Luebben, G. González-Parra, B. Cervantes, G. Luebben, G. González-Parra, et B. Cervantes, « Study of optimal vaccination strategies for early COVID-19 pandemic using an age-structured mathematical model: A case study of the USA », *Math. Biosci. Eng.*, vol. 20, nº 6, Art. nº mbe-20-06-481, 2023, doi: 10.3934/mbe.2023481.
[23] « Age Structured Mathematical Modeling Studies on COVID-19 with respect to Combined Vaccination and Medical Treatment Strategies ». https://www.degruyter.com/document/doi/10.1515/cmb-2022-0143/html?lang=en (consulté le 30 juin 2023).
[24] E. Aruffo *et al.*, « Mathematical modelling of vaccination rollout and NPIs lifting on COVID-19 transmission with VOC: a case study in Toronto, Canada », *BMC Public Health*, vol. 22, nº 1, p. 1349, juill. 2022, doi: 10.1186/s12889-022-13597-9.
[25] X. Liu et Y. Ding, « Stability and Numerical Simulations of a New SVIR Model with Two Delays on COVID-19 Booster Vaccination », *Mathematics*, vol. 10, nº 10, Art. nº 10, janv. 2022, doi: 10.3390/math10101772.
[26] H. W. Hethcote et P. Waltman, « Optimal vaccination schedules in a deterministic epidemic model », *Math. Biosci.*, vol. 18, nº 3, p. 365-381, déc. 1973, doi: 10.1016/0025-5564(73)90011-4.
[27] L. J. S. Allen, « An Introduction to Stochastic Epidemic Models », in *Mathematical Epidemiology*, F. Brauer, P. van den Driessche, et J. Wu, Éd., in Lecture Notes in Mathematics. Berlin, Heidelberg: Springer, 2008, p. 81-130. doi: 10.1007/978-3-540-78911-6_3.
[28] L. J. S. Allen, « A primer on stochastic epidemic models: Formulation, numerical simulation, and analysis », *Infect. Dis. Model.*, vol. 2, nº 2, p. 128-142, mars 2017, doi: 10.1016/j.idm.2017.03.001.
[29] P. E. Greenwood et L. F. Gordillo, « Stochastic Epidemic Modeling », in *Mathematical and Statistical Estimation Approaches in Epidemiology*, G. Chowell, J. M. Hyman, L. M. A. Bettencourt, et C. Castillo-Chavez, Éd., Dordrecht: Springer Netherlands, 2009, p. 31-52. doi: 10.1007/978-90-481-2313-1_2.
[30] F. Russo, « Stochastic Differential Equations », in *Encyclopedia of Mathematical Physics*, J.-P. Françoise, G. L. Naber, et T. S. Tsun, Éd., Oxford: Academic Press, 2006, p. 63-71. doi: 10.1016/B0-12-512666-2/00369-2.
[31] F. Zuhairoh, D. Rosadi, et A. R. Effendie, « Multi-state Discrete-time Markov Chain SVIRS Model on the Spread of COVID-19 », vol. 30, nº 2, 2022.
[32] H. J. Alsakaji, F. A. Rihan, et A. Hashish, « Dynamics of a Stochastic Epidemic Model with Vaccination and Multiple Time-Delays for COVID-19 in the UAE », *Complexity*, vol. 2022, p. e4247800, avr. 2022, doi: 10.1155/2022/4247800.
[33] R. Lu et F. Wei, « Persistence and extinction for an age-structured stochastic SVIR epidemic model with generalized nonlinear incidence rate », *Phys. Stat. Mech. Its Appl.*, vol. 513, p. 572-587, janv. 2019, doi: 10.1016/j.physa.2018.09.016.

[34] S. Moore, E. M. Hill, L. Dyson, M. J. Tildesley, et M. J. Keeling, « Modelling optimal vaccination strategy for SARS-CoV-2 in the UK », *PLOS Comput. Biol.*, vol. 17, n° 5, p. e1008849, mai 2021, doi: 10.1371/journal.pcbi.1008849.
[35] J. Arino et E. Milliken, « Bistability in deterministic and stochastic SLIAR-type models with imperfect and waning vaccine protection », *J. Math. Biol.*, vol. 84, n° 7, p. 61, juin 2022, doi: 10.1007/s00285-022-01765-9.
[36] J. J. de Wit et A. Deventer, « GUMBORO DISEASE: ESTIMATION OF OPTIMAL TIME OF VACCINATION BY THE DEVENTER FORMULA ».
[37] F. Jean-Yves et B. Catherine, « Détermination de la date de vaccination contre la maladie de Gumboro en élevage de poulets label. », 2005.
[38] « [No title found] », *Int. J. Curr. Microbiol. Appl. Sci.*.
[39] A. Essalah-Bennani, S. Nassik, M. Bouzouaia, et O. F. Fihri, « Cinétique des anticorps d'origine maternelle anti-virus de l'influenza aviaire faiblement pathogène H9N2 et interférence avec la vaccination chez le poulet de chair », *Rev. Marocaine Sci. Agron. Vét.*, vol. 9, n° 3, sept. 2021, Consulté le: 22 juin 2023. [En ligne]. Disponible sur: https://www.agrimaroc.org/index.php/Actes_IAVH2/article/view/1001
[40] R. H. Jacobson, « Factors in selecting serum samples for use in determining the positive/negative threshold (cut-off) in ELISA », nov. 1998, Consulté le: 22 juin 2023. [En ligne]. Disponible sur: https://www.osti.gov/etdeweb/biblio/298082