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Mathematical and game-theoretic modeling of malaria spread with and without vaccination

1.2.3. Theoretical informatics, cybernetics

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Contents

Introduction

Relevance of thesis topic

Infectious diseases continue to be a major problem in our society, killing millions of people every year. Over the past thirty years, 35 new infectious diseases [56] have appeared worldwide, 26 of which are of viral origin: HIV, legionellosis (caused by the bacterium *Legionella*), influenza virus $H5N1$, severe acute respiratory syndrome (*SARS*), Middle East respiratory Syndrome (*MERS*), Ebola virus, and more recently, humanity has faced pandemic disease *COVID-19*. There are just some of them, to name but a few. While some of these diseases make headline news, there is practically no information on other ones. Such diseases are also a big problem for society, that scientists, the public health system and medical organizations must solve.

Mathematical and game-theoretic modeling of malaria offers a tool for determining the dynamics of the disease development and working out possible measures to control pathogen transmission by mosquitoes. The models show that it is also necessary to use epidemiological and entomological actions for measuring the ways of disease transmission. Mathematical modeling allows to create programs to describe, analyze and predict disease spread in the real world. This approach is especially relevant for studying the disease spread in complex systems. The theory presented in the paper makes an important contribution to decision-making for the fight against a modeled disease, which involves a profound change in a complex system of interconnected biological objects. The evolutionary potential of parasites and vectors, increase and decrease in human immunity, behavioral changes in human and vector populations, and interactions within numerous and heterogeneous subpopulations of relevant organisms make it difficult to develop universal programs and policy for disease control.

The paper also proposes a model of economic interaction between companies pro-

ducing vaccines, which allows obtaining equilibrium prices in the market, assuming that companies can unite in coalitions of different sizes. The results obtained make it possible to define equilibrium strategies of market participants, as well as to analyze vaccine prices under various scenarios of cooperation between companies.

In general, the thesis is devoted to a theoretical and practical study of the dynamics of malaria development in society, as well as the study of the behavior of vaccine manufacturers in the market under various scenarios of cooperation. The research proposes several mathematical models that can be used in the healthcare system to analyze the disease in society, as well as to predict its further development in society.

Overview of the results in this area

When people think of the deadly diseases, they probably bear in mind rapidly spreading incurable diseases that appear from time to time in magazine and newspaper articles. But in fact, many of these diseases are not among the leading causes of mortality worldwide. Malaria is considered to be a dangerous disease. For decades, scientists have been developing strategies to stop rapidly spreading diseases. It became possible to find cures for such diseases as dengue fever, yellow fever, rabies, tuberculosis, etc. Despite these impressive achievements, there are still diseases against which vaccine effectiveness remains quite low, and malaria belongs to such diseases. Malaria is an ancient disease that causes great harm to people's health and entails great losses for society. The climate in tropical regions such as Africa, Asia, and America contributes to the rapid spread of this disease [28, 18]. Many attempts have been made to describe the complex dynamics of human (host) and insect (vector) populations with malaria infection using mathematical models. Until 1990s, it was one of the most deadly diseases in the world. According to the latest report of the World Health Organization (WHO), progress in malaria control is still low, especially in African countries with a high disease incidence[7]. In 2019, there were 229 million cases of malaria registed worldwide [7]. Over the last four years, this figure has remained virtually unchanged. The disease took about 411 thousand lives in 2018 and 409 thousand lives in 2019. Until now, many people all over the world continue suffering from malaria, especially in the tropics, subtropics, sub-Saharan Africa, in the countries of Asia, Latin America and the Middle East,

thereby prompting scientists to develop methods of fighting malaria or managing the disease. The classical population models developed by Ross and McDonald [58, 72] still form the basis for many new approaches [18, 59, 61]. These models are based on the SIR (susceptible/infected/recovered) model and aim at making epidemiological predictions. In addition to the models mentioned above, the study on malaria forecasting, the results of which are presented in this thesis, also relied on the development models of the *Covid-19* epidemic in Russia and other countries, as well as malaria in African countries [4, 3, 5, 8, 7, 32, 36, 55, 60, 76, 84, 85]. Many research groups are working on creating effective models and methods for forecasting the spread of viruses, but malaria is not an attractive topic for most scientists. The models allowing to understand the dynamics of spreading new viruses such as *Covid-19* have also been presented in well-known periodical scientific journals [84, 60, 36].

Scientists study diseases to help society overcome problems associated with them. Several methods have been used for malaria control. For example, in Africa traditional remedies developed by local experts were used. They study the virus in detail and offer response methods that can reduce the disease rate, prevent virus spread, try to invent a vaccine or an effective medicine [31]. The vaccine *RTS,S/AS01 (RTS, S)* proposed by the World Health Organization has a very low efficiency. The *RTS,S/AS01 (R, S)* vaccine that works against a causative agent of tropical malaria *Plasmodium falciparum*, a parasite that is a source of the world's most lethal form of malaria and mostly spread prevalent in Africa. According to WHO, the vaccine significantly reduces malaria disease, as well as its severe form with potentially dangerous effects on children's lives. Over the past ten years, the creation of malaria vaccines has been in clinical or preclinical development. Several clinical trials are currently being conducted, but no vaccine has shown a fairly high effectiveness. However, a certain level of clinical immunity against malaria can be achieved by vaccination. Vaccines affect the malaria vector at various stages of its life cycle. According to the effect of exposure and the type of immune response, vaccines can be divided into the groups:

1. Vaccines against stages of pre-erythrocytes,
2. Vaccines against asexual stages in blood,
3. Vaccines that block virus transmission.

Vaccine development uses mathematical models, mostly with differential equations, to have an idea of how the malaria epidemic passes and how effective the vaccine is. The parameter describing a percentage of the vaccinated population can change depending on a current situation in the society. The most popular epidemic model is the *SIR* model and its modifications [10]. This paper proposes a modified epidemic model of spreading malaria with vaccination, based on the *SEIR* model. In this thesis, the population is considered to be enclosed, in contrast to standard models, the transition from the population of recovered patients to the population of susceptible ones is taken into account (as in the case of malaria and as confirmed by medical research), and the level of vaccination of the population is also taken into consideration.

Mathematicians create mathematical models that make it possible to better understand the mechanism of disease spread and describe the epidemic process. Deterministic and stochastic models of population change are important for describing [3] processes, as well as for understanding the relationship between vector-borne diseases and ecological communities. A classic model for the epidemic spread is the one proposed by Ross *(1911)* and Macdonald *(1957)* [58, 77], who are considered to be the creators of the *SIR* model and its modifications. We note the work [7], which compares and calibrates the *SIR* model of the development of the epidemic process using real data on the disease *COVID-19*. The malaria cycle and its transmission between human secondary hosts and primary vectors of the genus *Anopheles* (mosquito) are complex. The female mosquito Anopheles transmits the disease to human body through a bite [54], as a result the individuals of the community are divided into categories according to the density of parasites within them and the type of infection. The dynamics of these subpopulations is presented using a modified $SAS_kE_kI_k$ model based on the pioneering work of Kermack and McKendrick [51]. The model of the disease onset and a complex process of transmitting infection from a person to a mosquito are difficult to model mathematically, and many assumptions and simplifications have to be done in modeling. Suffice it to say that malaria infection in humans begins when sporozoites are injected into the bloodstream by an infected female mosquito. Sporozoites migrate to the liver, and after some time (weeks or sometimes months later) they enter the bloodstream in the form of gametocytes, which the mosquito initially receives when biting by an infected person. As a result of the development cycle in the mosquito, the injected gametocytes become

gametes, which first develop into zygotes and then into motile ookinetes piercing mosquito gut and releasing a large number of sporozoites. The cycle ends.

This paper also proposes a deterministic model of a vector-borne disease. This model describes the process of disease transmission from mosquitoes to humans and from humans to mosquitoes, as described in the malaria cycle. Mathematically, the dynamics of subpopulations, taking into account such disease transmission, is described by a system of differential equations [7, 44, 86]. In turn, this model has allowed to create mathematical models of many other vector-borne diseases [26, 31, 38, 42, 46, 50, 70, 74, 79]. We also note the works [38, 70, 74, 79, 26, 42, 46, 50, 1, 31, 28, 59, 18], in which mathematical modeling of many other vector-borne diseases is based on similar epidemic models. Many infectious diseases are transmitted to the human population by vectors, and malaria is such a disease. The peculiarities of its transmission (blood transfusion, transplantation or exposure through a contaminated needle) are described in [83]. In this paper, it is assumed that direct transmission of the malaria virus can be neglected due to its low level of infection compared with the level of transmission from a mosquito, this greatly simplifies a mathematical model. This paper presents a mathematical model for the development of malaria, which sets the dynamics of the development of subpopulations in two interacting populations: humans and mosquitoes [65].

The paper summarizes some existing mathematical models for the development of malaria by including susceptible, infected, recovered humans, as well as subpopulations of susceptible and infected mosquitoes in the considered population, taking into account mortality caused by the disease in the population. The paper studies the stability of the system of differential equations describing the model, the analysis of which shows that there are equilibria that characterize the state of the system without a disease, and stable states in the presence of an epidemic. The basic reproduction number R_0, the number of secondary infections that an infectious individual could transmit during a disease period, is calculated, assuming that the entire population is susceptible, excluding those already infected. Disease control is possible only if the basic reproductive number R_0 is less than a threshold value. Thus, it is necessary to define and establish threshold values for a possible control of developing of infection in the community.

This work partly continues the work of [7], which proposed an epidemic model of malaria without vaccination. The thesis proposes a generalized model of the dy-

namics of malaria, taking into account the community of people who are exposed, infected, recovered, and also bearing in mind mortality that varies in different populations. In addition, the model represents the phenomenon of the existence of an equilibrium without an epidemic, this equilibrium is locally asymptotically stable, and there is also an endemic equilibrium when there is an epidemic in the society, and it is locally asymptotically stable when $R_0 \leq 1$. Using the theory of Lyapunov functions and the Routh–Hurwitz criteria, we study the problem of asymptotic stability of equilibria [41, 66]. It is proved that the overall dynamics of the system is completely determined by the value of R_0 [11, 24, 34, 49, 57, 66, 80]. If $R_0 \leq 1$, the state of the system when there is no disease is stable. If $R_0 \geq 1$, there is a unique endemic equilibrium, and it is globally asymptotically stable.

The paper presents a model of stochastic disease prediction based on the existing multivalued deterministic models of the type "susceptible — infected — recovered" (SIR) or "susceptible — exposed — infected — recovered" ($SEIR$) [32, 67], describing mechanisms of virus spread from person to person. In addition to various epidemiological models, various models and methods of time series analysis are used for forecasting [76]. Besides, the models based on machine learning methods began to appear. For example, the authors of the research [87] evaluated the effectiveness of the dynamic Bayesian network in epidemiological monitoring of infectious diseases. The paper [75] compares a statistical approach, which is often used in practice, and a case-based method proposed by the authors, which is more based on current data. They convincingly demonstrated the advantage of their method in predicting the dynamics of epidemic outbreaks, in which waves are characterized by irregular cycles and it is difficult to predict them using earlier epidemic statistics. Moreover, the first methods of mortality analysis were carried out in 1766 by D. Bernoulli [25] in order to influence the state vaccination policy to stop the spread of smallpox. It should be noted that the works of R. Ross, W. H. Hamer, W. O. Kermack, and A. G. Mackendrick [39, 51] made a significant contribution to epidemiological research. The models proposed by the above authors are deterministic, and it is possible to calculate the basic reproductive number R_0 for them, which determines the threshold between epidemic growth and decline. The proposed models, including the SIR model, have proven their effectiveness in modeling the spread of tuberculosis, AIDS, influenza, Ebola and malaria [23]. But the coronavirus pandemic, caused by the *SARS-CoV-2* virus, gave impetus to the development of mathematical modeling of

epidemics and creation of more complex models [48]. The articles [8, 7] present the models of malaria development in a population with and without vaccination, based on the $SEIR$ model. Another model proposed in this thesis is based on the work [4], which describes a new model for the development of the *Covid-19* epidemic and makes forecasts based on the available statistical data and the principle of dynamic balance of the epidemiological process formulated by the authors. In this paper, two models are used to build annual forecasts for the development of malaria epidemic: the modified SIR model and the $CIRD$ balance model, a comparative analysis is made to apply them in practice, namely for modeling malaria disease spreading in Senegal [6].

Studies show that vaccination is an excellent way to control the disease, therefore our work proposes a model of competition and cooperation between vaccine manufacturers. In this part of the thesis, a company interaction model is used, described by a differential game with infinite duration. Companies can unite in one big coalition or in smaller coalitions, which leads to the formation of a coalition structure [19]. Companies can choose whether to be members of a coalition or act individually. Coalition structures are applicable to many vital problems arising in political, economic, and social sciences, where most large coalitions cannot be formed for many reasons [37, 81, 69, 68]. Coalitions are formed on the basis of assumptions and rules clearly defined by decision makers in the respective companies. There is also a coalition structure in the paper, which is stable in some sense, and its formation can be considered as a stable state of the economy in this sector [68, 16, 73]. Obviously, one cooperation scenario may be more preferable for some companies than for others [69, 16, 73, 30]. Any company will want to participate in a certain coalition if its profit in this coalition is greater than in any other, or in the case when it deviates to become an individual player [73, 33, 78]. The study of the stability of coalition structures is carried out using the concept of Nash equilibrium [69, 78].

Goals of the thesis

In this work, one of the goals is to build generalized mathematical models of malaria spread, which take into account population mortality among subgroups, the possibility of transition from recovered to susceptible people, the presence or absence of vaccination of the population. Also, the purpose of the work is to analyze presented

models, find some equilibria, study their stability, and conduct numerical modeling of the results with their subsequent analysis of sensitivity to model parameters. Another goal of the work is to develop models of malaria spread for their application in practice to build forecasts for disease development. In this regard, the work propose two models, one of which is based on SIR, the other one is a stochastic model. In terms of forecasting, the best proposed model for making forecasts is the so-called balance model, which is confirmed by the forecasts made for malaria disease in Senegal. Another goal of the work is to create a model of competition and cooperation of vaccine companies to understand what equilibrium will be in the market, what production volume the companies will choose in equilibrium and with cooperation, which will undoubtedly affect buyers, and subsequently a course of the epidemic in society. Summarizing the above, a great goal of the work is to present mathematical tools for decision makers in the fight against malaria for adequate planning of social and economic policy, as well as the effective development of a set of anti-epidemiological measures.

Main tasks

One of the tasks that this research aims to solve is the construction of a mathematical model of malaria epidemic in the human (host) population, in which the disease is transmitted by a malarial mosquito, and this is taken into account in the model parameters. A malaria spread model is given by a system of ordinary differential equations. The host population at any given time is divided into four subpopulations: susceptible, exposed, infected, and recovered. It is required to obtain sufficient conditions for the stability of equilibrium without disease and endemic equilibrium using the theory of the Lyapunov functions, as well as to find the basic reproductive number that characterizes an epidemic course in a population. The task is also to build a similar model for malaria development, but taking into account the vaccination of the population, the study of equilibria on stability and the calculation of the basic reproductive number. It is necessary to conduct numerical modeling to study the effect of parameters on disease spread and to illustrate the theoretical results (for models with and without vaccination).

Another task of the work is to build a mathematical model of malaria epidemic with vaccination in a human population (host), when the disease is transmitted by

a mosquito (vector), in which both populations would be considered simultaneously, regardless if human population is vaccinated or not. The host population at any given time is divided into four subgroups: susceptible, exposed, infected, and recovered. It is required to obtain sufficient conditions for the stability of disease-free and endemic equilibrium and calculate the basic reproductive number, as well as perform numerical simulations to study the influence of model parameters, including the level of vaccination of the population, on disease spread in two populations.

In the thesis, the task is to build a mathematical model of malaria epidemic to predict the annual disease in Senegal based on the available data on disease from 2000 to 2021. The SIR and $CIRD$ models can be considered as basic models. The task is to construct a modified SIR model with constant coefficients and a $CIRD$ balance model with stochastic parameters. The question of accuracy of forecasting the annual statistical indicators of the epidemic when using these models is investigated. Numerical experiments show that the average forecasting error of the annual number of sick people in relation to the actual statistical data when using the SIR model is quite big, while the $CIRD$ model generates more accurate forecasts in a comparative analysis.

The paper also sets the task of creating a model of economic interaction (competition and cooperation) of companies that are manufacturers of vaccines. In the proposed model, companies should be able to unite in coalitions of any size, and the coalition will be considered as a separate player maximizing the total profit of the companies included in the coalition. For each cooperative scenario, it is possible to calculate the profit and production volumes of its members in equilibrium. The task is to find a stable coalition structure, in which no company will deviate from its coalition.

Scientific novelty

In this thesis, several generalized models of malaria spread in human population with and without vaccination among people are proposed. Models are developed taking into account the specifics of malaria spread in human population. For the presented models, the analysis of the stability of some equilibrium points was carried out, and the basic reproductive number was calculated. The paper also presents a model for malaria development simultaneously in two populations: humans and mosquitoes.

This model has been modified to take into account the impact of vaccination on the dynamics of malaria spread in populations. For these models, the stability of some equilibrium points of the system was also studied, and the expressions for the basic reproductive number in each population were obtained.

In the thesis, two epidemiological models were developed for their use in predicting malaria disease. The models are focused on the use of annual data, which is quite difficult since most practical models exploit daily or monthly data. The work used data on malaria disease in Senegal from 2020 to 2021. The first proposed model is a modification of the SIR model that is applied to discrete data. The second proposed model is a stochastic, modified $CIRD$ balance model. An undoubted scientific novelty is the adaptation of this method to forecasting using annual data, while earlier forecasting was carried out mainly using daily or monthly data. The paper gives a forecast for the next five years based on two proposed models, and concludes that the second model has the best predictive ability.

A model of dynamic interaction between companies producing vaccines is proposed. Various scenarios of cooperation are considered, when companies unite in coalitions of various sizes and composition, the issue of stability of coalition structures is studied in order to predict a stable state of the market and determine the market value of the vaccine. Companies that form coalitions are being studied. The profits of companies in a stable state of the market are determined, and conclusions are drawn about which structures are more preferable for consumers and companies.

Research methods

This thesis uses methods of mathematical modeling of epidemiological processes (building a model, finding solutions, numerical analysis), including methods of the theory of differential equations, studying the stability of system equilibrium points, calculating the basic reproductive number, optimization methods and game theory. In game-theoretic modeling, the theory of noncooperative and cooperative games, the theory of stability of coalition structures, the concept of Nash equilibrium are used. To solve differential games, Pontryagin's maximum principle is used in this work. Numerical modeling uses numerical methods for finding solutions to the systems of differential equations. Mathematical statistical methods, including descriptive statistics of the available data, are used to build predictive models of malaria

epidemic.

Theoretical and practical significance

The results presented in the thesis have theoretical significance for modern research epidemiology of vector-borne diseases. The models proposed in the paper can be applied in modeling the spread of new and existing infectious diseases in society. Based on the constructed models, it is possible to create a modern software product that allows numerical modeling for specific regions and countries. The importance of this study lies in the development of understanding of disease spread in the society, as well as in the possibility of applying various strategies necessary for reducing the rate of its spread.

The models developed by the author are of practical importance in building forecasts for the development of the epidemic in society. The specific results of such application are demonstrated in the third chapter of the thesis on the example of the state of Senegal. These results are of practical importance and can also be applied to the available data for other countries and regions.

Despite the fact that the presented models describe the development of malaria epidemic, they can be applied to other vector-borne diseases, taking into account the specifics of these diseases. Therefore, the scope of the obtained results can be quite extensive both in medical biology and in disease prevention.

The model of competition and cooperation of companies producing vaccines on the market, presented in Chapter 4, is of practical interest for studying the structure of a real vaccine market, as well as possible scenarios for cooperation of manufacturers. This undoubtedly affects consumers and the epidemiological situation as a whole.

Brief description of thesis structure

The thesis consists of an introduction, four chapters, a conclusion, a list of references and appendices. Each chapter begins with a description of a mathematical model, a list of notations used, and necessary definitions. Further, the obtained theoretical results for a specific model and the results of numerical simulation are presented to illustrate theoretical results and their analysis. A brief conclusion is provided at the end of each chapter.

The first chapter of the thesis is devoted to the epidemic model of malaria with

and without vaccination, built on the basis of the $SEIR$ model, when a mosquito population is not considered separately, and its impact on the dynamics of human population is set by the model parameters. The first part of this chapter is devoted to building a model of malaria without vaccination, and has the following structure. Section 1.1.1 provides the formulation of a mathematical model for malaria epidemic. Section 1.1.2 defines the region of acceptable values. Section 1.1.3 studies two equilibria of the system. The basic reproductive number R_0 for the proposed model is defined in section 1.1.4. Section 1.1.5 provides a mathematical analysis of the stability of the equilibrium points of the proposed model. Numerical modeling is described in Section 1.1.6. The second part of the first chapter deals with a similar model of malaria, but with vaccination. This section is structured as follows: Section 1.2.1 proposes a malaria epidemic model with vaccination. The equilibrium points for the described model with vaccination are studied in Section 1.2.2. The study of the stability of equilibrium points is described in Section 1.2.3. Numerical simulations is described in Section 1.2.4. Numerical modeling and the analysis of the impact of vaccination on the population is given in Section 1.2.5. The conclusion to the first chapter is given in Section 1.2.6.

The second chapter of the thesis is devoted to epidemic model of transmissible malaria, which describes the dynamics of disease spread in two populations: humans and mosquitoes. This chapter has several sections. The description of the model and the range of values are described in Section 2.1.1. Section 2.1.2 defines the equilibrium points of the system of differential equations and finds the basic reproductive number R_0, and then studies the stability of the system at the equilibrium points. The results of numerical modeling are given in Section 2.1.3. The chapter ends with a brief review of the results.

The third chapter of the thesis is devoted to two more epidemiological models of malaria and their practical use for making forecasts based on available data. This chapter is structured as follows. A description of the data sampling is given in Section 3.1. Section 3.2 builds a modified SIR model based on statistical data and then builds a forecast of malaria epidemic in Senegal from 2000 to 2016 and from 2000 to 2021 as described in Sections 3.2.1 and 3.2.2. Section 3.3 proposes a balance model for malaria which is described in terms of percentage increase in Section 3.3.1. Section 3.3.2 explores the practical application of the model. Finally, the model forecasts from 2011 to 2017, from 2018 to 2021, and from 2021 to 2027

are presented in Sections 3.3.3, 3.3.4 and 3.3.5 respectively. A brief conclusion to the third chapter is given in Section 3.4.

The fourth chapter of the thesis is devoted to the study of competition and cooperation of vaccine manufacturing companies described by a differential coalitional game with infinite duration, where each company tries to maximize its profit by choosing the production volume. This chapter is divided into sections. Section 4.1 describes a game-theoretic model. Section 4.2 formulates the main theoretical results on Nash equilibrium in games with various coalition structures. The definition of the stability of a coalition structure is given in Section 4.3. A numerical example is presented in Section 4.4. Section 4.5 contains a brief conclusion to the chapter.

Results submitted for defense

Let us formulate the main results obtained in the work:

1. A modified $SEIR$ malaria spread model is proposed without taking into account the dynamics of mosquito population, but taking into consideration the fixed exposure of malaria-infected mosquitoes to human population with or without vaccination in human population. The stability of some equilibrium points of the system has been studied, the basic reproductive number R_0 has been found, and numerical modeling has been carried out using different values of parameters and, accordingly, different values of the basic reproductive number R_0.

2. A generalized model of malaria spread $SEIRS_kE_kI_k$ has been built, which describes the dynamics of two interrelated populations: humans and mosquitoes. The proposed model has two modifications: with and without vaccination. For both models, some equilibria of the system are found, the stability of these equilibria is investigated, the basic reproductive number is found, and numerical modeling is carried out using various values of parameters.

3. Models for predicting malaria epidemic based on available annual statistical data using the SIR model and the $CIRD$ model are proposed. The main feature of the proposed models, in contrast to classical versions, is their suitability for modeling over time intervals, the length of which (one year) significantly exceeds the duration of the disease. The predicted values are compared with

the actual data presented in an integrated form for various time intervals, the average approximation errors are obtained, on the basis of which a conclusion is made about the possibility of using the model to predict the number of active cases and the total number of recovered. One of the models is based on the principle of dynamic balance of the epidemiological process and takes into account when making forecasts the generated dynamic trends of stochastic values of a percentage increase in the total number of diseased cases and assumptions about stationary or nonstationary nature of the change in the characteristics of dynamic balance.

4. A model of competition and cooperation of companies producing vaccines has been proposed, within which various options for cooperation of companies have been studied. For each possible coalition, the profits and production volumes of its participants are determined. An analysis of the stability of possible coalition structures or scenarios of cooperation of companies was carried out, and coalition structures were found that are most attractive to consumers.

Verification of results

The main results of the thesis were published in high-ranking scientific journals (Bulletin of Saint Petersburg State University. Applied Mathematics and Informatics, Mathematical Game Theory and its Applications, Contributions to Games and Management), and the results were presented at international conferences: "Control Processes and Sustainability" (2021, 2022), "SCIENCE SPBU — 2022", International conference "Game Theory and Management" (Saint Petersburg, 2023). The results of the thesis were reported at the seminars of the Department of Mathematical Game Theory and Statistical Solutions of Saint Petersburg State University.

Publications

The results of the work were published in four articles in international peer-reviewed scientific journals and in several abstracts at scientific conferences of Saint Petersburg State University.

Acknowledgments

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I am also grateful to the Government of the Republic of Senegal, which has given me its trust, and to the Government of the Russian Federation, which has provided me with a scholarship for the entire period of my study in the Russian Federation. I cannot even list all those who are near and far from me now, to whom I would like to express my gratitude, to those who helped me in writing this work. Thank you all.

Chapter 1

Epidemic model of malaria without and with vaccination

This chapter proposes a mathematical model of the malaria epidemic in the human (host) population, where the disease is transmitted by the malaria vector mosquito (vector) [4]. First, we consider a model without no vaccination [3]. The malaria distribution model is given by a system of ordinary differential equations. The host population at any given time is divided into four subpopulations: susceptible, exposed, infected, and recovered. Sufficient conditions for the stability of equilibrium without disease and endemic equilibrium are obtained using the theory of the Lyapunov function. The basic reproductive number, characterizing the course of the epidemic in the population, has been found. Numerical simulations are performed to study the effect of model parameters on the disease spread and the theoretical results are shown in the illustrations. Besides, in this chapter, we present a modification of the model, which takes into account the level of vaccination in the population. The results similar to those described above are obtained. The influence of the level of vaccination on the disease spread is studied.

1.1 Model of malaria without vaccination

In this section, we investigate the spread of malaria in the human population, where the mosquito population is represented as a model parameter.

1.1.1 An epidemic model of malaria

A diagram illustrating the spread of malaria in a population based on a modified $SEIR$ model is shown in Fig. 1.1. Suppose there are two populations: human (*host*)

and mosquito (*vector*) [7, 8, 13, 24, 25]. A healthy host can be infected with the virus only one way, by the mosquito bite. An infected host can transmit the infection to a susceptible mosquito that will bite it. The density and development dynamics of the host and vector populations are very different. The vector population is much larger than the host population and its lifespan is much shorter. We propose a model of host population dynamics at the constant number of infected mosquitos.

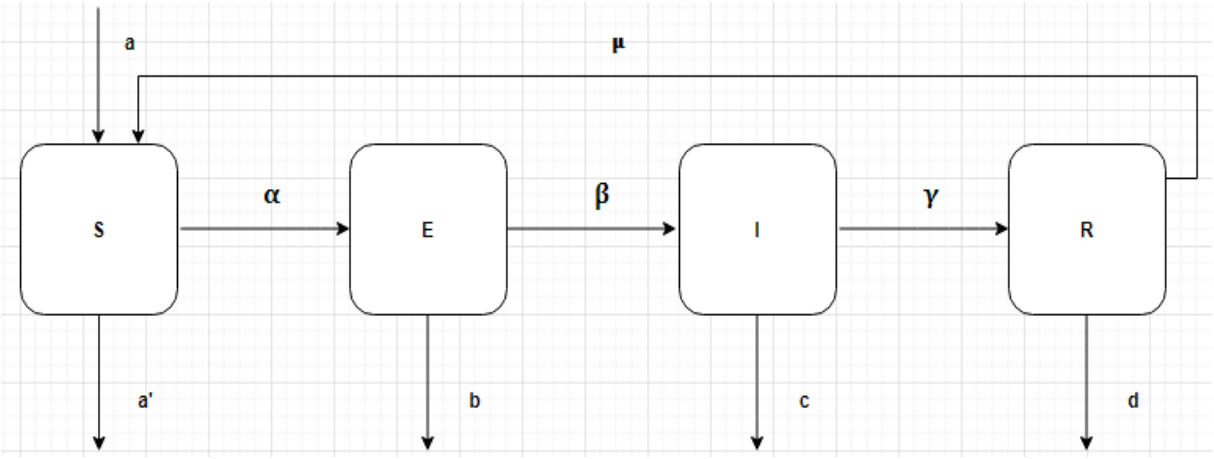

Figure 1.1: Malaria model $SEIR$

The host population at any given time t is divided into four subpopulations: susceptible host $S(t)$, exposed host $E(t)$, infected host $I(t)$, and recovered host $R(t)$ with the total population $N(t) = S(t) + E(t) + I(t) + R(t)$. The proposed dynamic model of the malaria spread differs from existing models as follows:

1. In comparison with many existing mathematical models, a subpopulation of those exposed by a mosquito, denoted by $E(t)$, has been added.

2. Mortality rates in the host population are different for various subpopulations and denoted by a', b, c, d for subpopulations $S(t)$, $E(t)$, $I(t)$, $R(t)$ respectively. We can assume that $a', b, d < c$. In many existing models, the coefficients a', b, d are assumed to be equal.

3. Transition coefficients from one subpopulation to another are denoted by α, β, γ and μ respectively (Fig. 1.1).

4. The total size of the host population changes over time and is equal to $N(t) = S(t) + E(t) + I(t) + R(t)$ at time t.

5. The intensity of transition from the recovered to susceptible subpopulation is positive, i.e., the immunity acquired after recovery from malaria is not stable.

In addition, this possible transition is due to the presence of several species of mosquitoes transmitting malaria in the same region.

The model uses the following parameters:

- $N(t)$ — size of human population;
- $S(t)$ — size of subpopulation of susceptible people;
- $E(t)$ — size of subpopulation of people exposed by mosquito;
- $I(t)$ — size of subpopulation of infected people;
- $R(t)$ — size of subpopulation of recovered people;
- a — birth rate in human population;
- a' — mortality rate among subpopulation S;
- b — mortality rate among subpopulation E;
- c — mortality rate among infected subpopulation I;
- d — mortality rate among recovered subpopulation R;
- α_1 — intensity of bites per person by one mosquito (defined as the number of bites per unit of time);
- α_2 — rate of bites of malaria-infected mosquitoes;
- β — rate of people's transition from subpopulation E to I, i.e. with the symptoms of the onset disease;
- γ — rate of people's recovery, i.e. the transition from subpopulation I to R;
- μ — rate of people's return from recovered to susceptible.

The mathematical model of subpopulation dynamics can be represented analytically by the following nonlinear system of four ordinary differential equations:

$$\begin{cases} \dfrac{dS(t)}{dt} &= -\alpha S(t)I(t) + aN_0 + \mu R(t) - a'S(t), \\ \dfrac{dE(t)}{dt} &= \alpha S(t)I(t) - bE(t) - \beta E(t), \\ \dfrac{dI(t)}{dt} &= \beta E(t) - cI(t) - \gamma I(t), \\ \dfrac{dR(t)}{dt} &= \gamma I(t) - dR(t) - \mu R(t), \end{cases} \tag{1.1}$$

where $\alpha = \frac{\alpha_1\alpha_2}{N_0}$. In this same time, the parameter α_2, equal to the rate of bites of malaria-infected mosquitoes, plays a primary role in the ratio between the proportions of susceptible and exposed subpopulations.

The initial conditions for the system of equations (1.1) are:

$$S(0) \geq 0, \quad E(0) \geq 0, \quad I(0) \geq 0, \quad R(0) \geq 0, \tag{1.2}$$

which provide the initial condition for the total size of the host population: $N(0) = N_0 = S(0) + E(0) + I(0) + R(0) \geq 0$. It can also be seen that the equation of population dynamics has the following form

$$\frac{dN(t)}{dt} = N_0 + aN(t) - a'S(t) - bE(t) - cI(t) - dR(t).$$

1.1.2 Study of region of admissible values

Assume that the size of population $N(t)$ must remain positive and bounded [1] for any $t \geq 0$. In the following statement, the set of admissible values being the solution of system (1.1) with initial conditions (1.2) is presented.

Proposition 1.1. *Let (S, E, I, R) be a solution of the system of differential equations* (1.1) *with initial conditions* (1.2), $\Omega = \left\{(S, E, I, R) \in \mathbb{R}^4_+, V_1 \leq N_0, V_2 \leq \frac{\alpha_1\alpha_2}{b+\beta}N_0, V_3 \leq \frac{\alpha_1\alpha_2\beta}{(b+\beta)(c+\gamma)}N_0, V_4 \leq \frac{\alpha_1\alpha_2\beta\gamma}{(b+\beta)(c+\gamma)(d+\mu)}N_0\right\}$ *is a closed set. Then Ω is positively invariant and absorbing for the system* (1.1) *with initial conditions* (1.2).

Proof. To study stability, we introduce the Lyapunov vector function $V(t)$:

$$V(t) = (V_1(t), V_2(t), V_3(t), V_4(t)).$$

Suppose that functions $V_1(t)$, $V_2(t)$, $V_3(t)$, $V_4(t)$ defined for $\forall\ t \geq 0$, are differentiable and continuously differentiable on the set Ω containing the origin.

Let us define the derivative of function $V(t)$:

$$\frac{dV(t)}{dt} = \begin{cases} \frac{dV_1(t)}{dt} &= N_0 - V_1(t) - a'S(t), \\ \frac{dV_2(t)}{dt} &= \alpha_1\alpha_2 N_0 - (b+\beta)V_2(t) - bE(t), \\ \frac{dV_3(t)}{dt} &= \alpha_1\alpha_2\beta N_0 - (b+\beta)(c+\gamma)V_3(t) - cI(t), \\ \frac{dV_4(t)}{dt} &= \alpha_1\alpha_2\beta\gamma N_0 - (b+\beta)(c+\gamma)(d+\mu)V_4(t) - dR(t). \end{cases} \tag{1.3}$$

[1] For reference, see [14]

From the system (1.3) it is obvious that

$$\begin{cases} \frac{dV_1}{dt} & \leq & N_0 - V_1, \\ \frac{dV_2}{dt} & \leq & \alpha_1\alpha_2 N_0 - (b+\beta)V_2, \\ \frac{dV_3}{dt} & \leq & \alpha_1\alpha_2\beta N_0 - (b+\beta)(c+\gamma)V_3, \\ \frac{dV_4}{dt} & \leq & \alpha_1\alpha_2\beta\gamma N_0 - (b+\beta)(c+\gamma)(d+\mu)V_4. \end{cases} \tag{1.4}$$

By the properties of the Lyapunov function, we obtain the following conditions:

$$\begin{cases} \frac{dV_1}{dt} & \leq & N_0 - V_1 \leq 0 \ \text{ for } \ V_1 \geq N_0, \\ \frac{dV_2}{dt} & \leq & \alpha_1\alpha_2 N_0 - (b+\beta)V_2 \leq 0 \ \text{ for } \ V_2 \geq \frac{\alpha_1\alpha_2}{b+\beta}N_0, \\ \frac{dV_3}{dt} & \leq & \alpha_1\alpha_2\beta N_0 - (b+\beta)(c+\gamma)V_3 \leq 0 \ \text{ for } \ V_3 \geq \frac{\alpha_1\alpha_2\beta}{(b+\beta)(c+\gamma)}N_0, \\ \frac{dV_4}{dt} & \leq & \alpha_1\alpha_2\beta\gamma N_0 - (b+\beta)(c+\gamma)(d+\mu)V_4 \leq 0 \ \text{ for} \\ V_4 & \geq & \frac{\alpha_1\alpha_2\beta\gamma}{(b+\beta)(c+\gamma)(d+\mu)}N_0. \end{cases} \tag{1.5}$$

It follows from the conditions (1.5) that $\frac{dV(t)}{dt} \leq 0$. This means that Ω is a positively invariant and absorbing set.

From the above equations and inequalities (1.3)–(1.5) and using Maple software, we derive inequalities for V_1, V_2, V_3 and V_4:

$$\begin{aligned} &0 \leq V_1(t) \leq N_0 + e^{-t}(V_{0_1} - N_0), \\ &0 \leq V_2(t) \leq \frac{\alpha_1\alpha_2 N_0}{b+\beta} + e^{-(b+\beta)t}\left(V_{0_2} - \frac{\alpha_1\alpha_2 N_0}{b+\beta}\right), \\ &0 \leq V_3(t) \leq \frac{\alpha_1\alpha_2\beta N_0}{(b+\beta)(c+\gamma)} + e^{-(b+\beta)(c+\gamma)t}\left(V_{0_3} - \frac{\alpha_1\alpha_2\beta N_0}{(b+\beta)(c+\gamma)}\right), \\ &0 \leq V_4(t) \leq \frac{\alpha_1\alpha_2\beta\gamma N_0}{(b+\beta)(c+\gamma)(d+\mu)} + \\ &+e^{-(b+\beta)(c+\gamma)(d+\mu)t}\left(V_{0_4} - \frac{\alpha_1\alpha_2\beta\gamma N_0}{(b+\beta)(c+\gamma)(d+\mu)}\right). \end{aligned}$$

For $t \longrightarrow +\infty$ we find that

$$\begin{aligned}
&0 \leq V_1(t) \leq N_0,\\
&0 \leq V_2(t) \leq \frac{\alpha_1\alpha_2 N_0}{b+\beta},\\
&0 \leq V_3(t) \leq \frac{\alpha_1\alpha_2\beta N_0}{(b+\beta)(c+\gamma)},\\
&0 \leq V_4(t) \leq \frac{\alpha_1\alpha_2\beta\gamma N_0}{(b+\beta)(c+\gamma)(d+\mu)}.
\end{aligned}$$

Then we can conclude that Ω is an absorbing set.

Indeed, as $t \longrightarrow +\infty$ we have inequalities

$$\begin{aligned}
&\limsup_{t\to+\infty} V_1 \leq N_0,\\
&\limsup_{t\to+\infty} V_2 \leq \frac{\alpha_1\alpha_2}{b+\beta}N_0,\\
&\limsup_{t\to+\infty} V_3 \leq \frac{\alpha_1\alpha_2\beta}{(b+\beta)(c+\gamma)}N_0,\\
&\limsup_{t\to+\infty} V_4 \leq \frac{\alpha_1\alpha_2\beta\gamma}{(b+\beta)(c+\gamma)(d+\mu)}N_0.
\end{aligned}$$

We get that Ω is a positively invariant and absorbing set for the system (1.1) with initial conditions (1.2). We will study the dynamics of this epidemic model on set Ω. □

1.1.3 Equilibrium points

Let us describe two equilibrium points (disease-free and endemic) of the dynamic system represented by equations (1.1) with initial conditions (1.2). To determine the equilibrium points of system (1.1) we solve the following system:

$$\left\{\begin{array}{rcl}
-\frac{\alpha_1\alpha_2}{N_0}S(t)I(t) + aN_0 + \mu R(t) - a'S(t) &=& 0,\\
\frac{\alpha_1\alpha_2}{N_0}S(t)I(t) - bE(t) - \beta E(t) &=& 0,\\
\beta E(t) - cI(t) - \gamma I(t) &=& 0,\\
\gamma I(t) - dR(t) - \mu R(t) &=& 0.
\end{array}\right. \tag{1.6}$$

As a result, we obtain equilibrium points, which will be studied in details as follows:

1. Equilibrium point of disease-free system $E_s = (N_0, 0, 0, 0)$, i.e., it is a constant solution of disease-free system;

2. Endemic equilibrium point of system $E_e = (S^*, E^*, I^*, R^*)$.

To find it, from the second equation of system (1.6) we get $S = \dfrac{(b+\beta)E}{\alpha_1\alpha_2 I}$, And we obtain $E = \dfrac{c+\gamma}{\beta}I$ from the third equation as well as, $R = \dfrac{\gamma}{d+\mu}I$ from the fourth one. According to the results of the second and third equations of (1.6) we find that $S = \dfrac{(b+\beta)(c+\gamma)}{\alpha_1\alpha_2\beta}$.

Substituting the above obtained expressions S and R into the first equation of the system, we obtain that

$$I = \frac{aN_0\beta(d+\mu)}{(b+\beta)(c+\gamma)(d+\mu) - \mu\gamma\beta}\Big(1 - \frac{a'(b+\beta)(c+\gamma)}{aN_0\alpha_1\alpha_2\beta}\Big).$$

Therefore, the endemic equilibrium of (1.1) is $E_e = (S^*, E^*, I^*, R^*)$ with components

$$\begin{aligned}
S^* &= \frac{(b+\beta)(c+\gamma)}{\alpha_1\alpha_2\beta}, \\
E^* &= \frac{c+\gamma}{\beta}I^*, \\
I^* &= \frac{aN_0\beta(d+\mu)}{(b+\beta)(c+\gamma)(d+\mu) - \mu\gamma\beta}\left(1 - \frac{a'(b+\beta)(c+\gamma)}{aN_0\alpha_1\alpha_2\beta}\right), \\
R^* &= \frac{\gamma}{d+\mu}I^*.
\end{aligned}$$

E_e represents the endemic equilibrium point of the model, in which a part of the population is infected, and also another part of the population which is on the way to recovery. The speed of recovery depends on the severity of the disease and the strategies adopted to eliminate the disease.

1.1.4 Determining the base reproduction number R_0

Let us determine the base reproductive number R_0 for a modified $SEIR$ model, which is taken as the basis for modeling the epidemic process. This number is used to study the evolution of the epidemic process and equal to the expected number of secondary cases caused by a primary infection in a fully susceptible population. It is important to note that R_0 is a dimensionless number. Appendix B describes methods for calculating the basic reproductive number.

To find R_0, we construct matrix G of the next generation, in which the (i,j)-th element g_{ij} represents the expected number of secondary infections of type i caused by one infected individual of type j, provided that the population of type i is completely

susceptible. In other words, each element of matrix G is a reproductive number, but data on who infects whom are taken into account. The base reproduction number depends on a spectral radius of matrix G.

Using the next generation method, we determine matrices F and V by making the following calculations:

$$\mathcal{F} = \begin{pmatrix} \frac{\alpha_1\alpha_2}{N_0} S(t)I(t) \\ 0 \\ 0 \\ 0 \end{pmatrix}, \mathcal{V}^+ = \begin{pmatrix} 0 \\ \beta E(t) \\ aN_0 + \mu R(t) \\ \gamma I(t) \end{pmatrix}, \mathcal{V}^- = \begin{pmatrix} -(b+\beta)E(t) \\ -(c+\gamma)I(t) \\ -\frac{\alpha_1\alpha_2}{N_0} S(t)I(t) - a'S(t) \\ -(\mu+d)R(t) \end{pmatrix},$$

hence we get that

$$\mathcal{V} = \mathcal{V}^+ + \mathcal{V}^- = \begin{pmatrix} -(b+\beta)E(t) \\ \beta E(t) - (c+\gamma)I(t) \\ aN_0 + \mu R(t) - \frac{\alpha_1\alpha_2}{N_0} S(t)I(t) - a'S(t) \\ \gamma I(t) - (\mu+d)R(t) \end{pmatrix}.$$

Find matrices

$$D\mathcal{F}(E_s) = \begin{pmatrix} 0 & \alpha_1\alpha_2 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad D\mathcal{V}(E_s) = \begin{pmatrix} -(b+\beta) & 0 & 0 & 0 \\ \beta & -(c+\gamma) & 0 & 0 \\ 0 & -\alpha_1\alpha_2 & -a' & \mu \\ 0 & \gamma & 0 & (\mu+d) \end{pmatrix}.$$

Hence,

$$F = \begin{bmatrix} 0 & \alpha_1\alpha_2 \\ 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} -(b+\beta) & 0 \\ \beta & -(c+\gamma) \end{bmatrix}.$$

Calculate G by formula $G = FV^{-1}$, where

$$V^{-1} = \frac{1}{det(V)} t_{(com(V))}, \quad det(V) = (b+\beta)(c+\gamma),$$

$$t_{(com(V))} = \begin{bmatrix} -(c+\gamma) & 0 \\ -\beta & -(b+\beta) \end{bmatrix}.$$

Finally, we obtain the equations

$$G = FV^{-1} = \begin{bmatrix} -\frac{\alpha_1\alpha_2\beta}{(b+\beta)(c+\gamma)} & -\frac{\alpha_1\alpha_2}{c+\gamma} \\ 0 & 0 \end{bmatrix},$$

$$R_0 = \rho(-G) = \rho(-FV^{-1}) = \frac{\alpha_1\alpha_2\beta}{(b+\beta)(c+\gamma)}.$$

If $R_0 \leq 1$ and at least one person is infected and the infection cannot develop, the system is said to be stable. If $R_0 \geq 1$, then the number of infected people increases and the disease can spread to the population. A numerical study will give us a clearer picture of the disease spread in the population relative to number R_0.

Note that an endemic equilibrium point E_e exists if $R_0 > 1$.

1.1.5 Study of stability of equilibrium points

The following statement represents the conditions for local stability of the equilibrium point without diseases.

Proposition 1.2. *The disease-free equilibrium point $E_s = (N_0, 0, 0, 0)$ is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof. Jacobi matrix corresponding to the system (1.1), has the form:

$$J(S,E,I,R) = \begin{pmatrix} -\frac{\alpha_1\alpha_2}{N_0}I - a' & 0 & -\frac{\alpha_1\alpha_2}{N_0}S & \mu \\ \frac{\alpha_1\alpha_2}{N_0}I & -b-\beta & \frac{\alpha_1\alpha_2}{N_0}S & 0 \\ 0 & \beta & -c-\gamma & 0 \\ 0 & 0 & \gamma & -d-\mu \end{pmatrix}$$

and at point E_s is equal to

$$J(E_s) = \begin{pmatrix} -a' & 0 & -\alpha_1\alpha_2 & \mu \\ 0 & -b-\beta & \alpha_1\alpha_2 & 0 \\ 0 & \beta & -c-\gamma & 0 \\ 0 & 0 & \gamma & -d-\mu \end{pmatrix}.$$

Let's find the eigenvalues of this matrix by equating the following determinant to zero:

$$\begin{vmatrix} -a'-\lambda & 0 & -\alpha_1\alpha_2 & \mu \\ 0 & -b-\beta-\lambda & \alpha_1\alpha_2 & 0 \\ 0 & \beta & -c-\gamma-\lambda & 0 \\ 0 & 0 & \gamma & -d-\mu-\lambda \end{vmatrix} = 0.$$

We get the equation

$$(a'+\lambda)(d+\mu+\lambda)[(b+\beta+\lambda)(c+\gamma+\lambda) - \beta\alpha_1\alpha_2] = 0.$$

We find two roots: $\lambda_1 = -a'$ and $\lambda_2 = -(d+\mu)$. Let's determine two more roots λ_3 and λ_4 by solving a second-degree equation:

$$\lambda^2 + (b+c+\beta+\gamma)\lambda + (b+\beta)(c+\gamma) - \beta\alpha_1\alpha_2 = 0,$$

which we rewrite in the form:

$$\lambda^2 + A\lambda + B = 0,$$

where $A = b + c + \beta + \gamma$, $B = (b + \beta)(c + \gamma) - \beta\alpha_1\alpha_2$. The determinant is $\Delta = A^2 - 4B$.

Consider all possible cases:

1. If $\Delta = 0$, we get a negative real eigenvalue, so the disease-free equilibrium E_s is locally stable.

2. If $\Delta > 0$, we get the roots:

$$\lambda_3 = -\frac{A + \sqrt{\Delta}}{2} = -\frac{A + \sqrt{A^2 - 4B}}{2}, \qquad \lambda_4 = \frac{-A + \sqrt{\Delta}}{2} = \frac{-A + \sqrt{A^2 - 4B}}{2}.$$

Note that signs of λ_3 and λ_4 depend on sign of B. We discuss such cases:

a) if $B > 0$, i.e. $(b + \beta)(c + \gamma) - \beta\alpha_1\alpha_2 > 0$ ($R_0 < 1$), then

$$\lambda_3 < -\frac{A + \sqrt{A^2}}{2} = -A < 0, \qquad \lambda_4 < \frac{-A + \sqrt{A^2}}{2} = 0.$$

Thus, all eigenvalues are negative;

б) if $B < 0$, i.e. $(b + \beta)(c + \gamma) - \beta\alpha_1\alpha_2 < 0$ ($R_0 > 1$), then

$$\lambda_3 = -\frac{A + \sqrt{A^2 - 4B}}{2} < 0, \qquad \lambda_4 = \frac{-A + \sqrt{A^2 - 4B}}{2} > 0.$$

There is a positive eigenvalue.

Disease-free equilibrium E_s is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

3. If $\Delta < 0$, we get two eigenvalues with negative real parts, so disease-free equilibrium E_s is locally stable. □

The following statement represents the local stability conditions for endemic equilibrium E_e.

Proposition 1.3. *A locally asymptotically stable endemic equilibrium point is equal to* $E_e = (S^*, E^*, I^*, R^*)$ *if* $R_0 > 1$ *and*

$$\frac{((b + \beta)(c + \gamma)(d + \mu) - \mu\gamma\beta)(b + c + d + \beta + \gamma + \mu + a') + \alpha_1\alpha_2 a N_0(d + \mu)}{a'(b + \beta)(c + \gamma)(d + \mu)} > 1.$$

Proof. . The Jacobi matrix corresponding to system (1.1) has the form:

$$J(S,E,I,R)=\begin{pmatrix} -\frac{\alpha_1\alpha_2}{N_0}I-a' & 0 & -\frac{\alpha_1\alpha_2}{N_0}S & \mu \\ \frac{\alpha_1\alpha_2}{N_0}I & -b-\beta & \frac{\alpha_1\alpha_2}{N_0}S & 0 \\ 0 & \beta & -c-\gamma & 0 \\ 0 & 0 & \gamma & -d-\mu \end{pmatrix}$$

and at point $E_e=(S^*,E^*,I^*,R^*)$ appears as

$$J(E_e)=\begin{pmatrix} -\frac{\alpha_1\alpha_2}{N_0}I^*-a' & 0 & -\frac{\alpha_1\alpha_2}{N_0}S^* & \mu \\ \frac{\alpha_1\alpha_2}{N_0}I^* & -b-\beta & \frac{\alpha_1\alpha_2}{N_0}S^* & 0 \\ 0 & \beta & -c-\gamma & 0 \\ 0 & 0 & \gamma & -d-\mu \end{pmatrix}.$$

Let us find the eigenvalues of this matrix by equating its determinant to zero. We get the equation

$$\lambda^4+A_1\lambda^3+A_2\lambda^2+A_3\lambda+A_4=0,$$

in which

$$\begin{aligned} A_1&=b+c+d+\beta+\gamma+\mu+a'+\frac{\alpha_1\alpha_2}{N_0}I^*,\\ A_2&=(a'+\frac{\alpha_1\alpha_2}{N_0}I^*)(b+c+d+\beta+\gamma+\mu)+d+\mu-\beta\frac{\alpha_1\alpha_2}{N_0}S^*,\\ A_3&=\frac{\alpha_1^2\alpha_2^2}{N_0}S^*I^*(1-\frac{\beta}{N_0})-\frac{\beta\alpha_1\alpha_2a'}{N_0}S^*+\\ &\quad+(d+\mu)((a'+\frac{\alpha_1\alpha_2}{N_0}I^*)(b+c+d+\beta+\gamma+\mu)-\frac{\beta\alpha_1\alpha_2}{N_0}S^*),\\ A_4&=(\frac{\alpha_1^2\alpha_2^2}{N_0}S^*I^*(1-\frac{\beta}{N_0})-\frac{\beta\alpha_1\alpha_2}{N_0}S^*a')(d+\mu)+\frac{\mu\beta\gamma\alpha_1\alpha_2}{N_0}I^*. \end{aligned}$$

The characteristic equation has four solutions, which are eigenvalues of matrix $J(E_e)$.

Equilibrium E_e is asymptotically stable if

$$\begin{aligned} A_1>0,\\ A_4>0,\\ A_1A_2-A_3>0,\\ A_3(A_1A_2-A_3)-A_1^2A_4>0, \end{aligned}$$

where A_1, A_2, A_3, A_4 are defined above.

It is easy to prove by applying the Routh-Hurwitz criterion. We write an auxiliary matrix

$$\begin{vmatrix} 1 & A_2 & A_4 & 0 & 0 \\ A_1 & A_3 & 0 & 0 & 0 \\ \dfrac{A_1A_2 - A_3}{A_1} & A_4 & 0 & 0 & 0 \\ \dfrac{A_3(A_1A_2 - A_3) - A_1^2A_4}{A_1A_2 - A_3} & 0 & 0 & 0 & 0 \\ A_4 & 0 & 0 & 0 & 0 \end{vmatrix}.$$

Applying the Routh-Hurwitz criterion, we obtain that system (1.1) is asymptotically stable at the equilibrium point E_e if the following inequalities hold

$$\begin{aligned} A_1 &> 0, \\ A_4 &> 0, \\ \frac{A_1A_2 - A_3}{A_1} &> 0, \\ \frac{A_3(A_1A_2 - A_3) - A_1^2A_4}{A_1A_2 - A_3} &> 0. \end{aligned}$$

From $\frac{A_1A_2 - A_3}{A_1} > 0$ and $A_1 > 0$ it follows that $A_1A_2 - A_3 > 0$. The fourth inequality is equivalent to $A_3(A_1A_2 - A_3) - A_1^2A_4 > 0$.

Therefore, we get the system:

$$\begin{aligned} A_1 &> 0, \\ A_4 &> 0, \\ A_1A_2 - A_3 &> 0, \\ A_1A_2A_3 - A_3^2 - A_1^2A_4 &> 0. \end{aligned}$$

Eigenvalues have negative real parts if they satisfy the Routh-Hurwitz criteria. Thus, all eigenvalues of a characteristic equation have negative real parts if and only if $R_0 > 1$ and $A_1A_2A_3 > A_3^2 - A_1^2A_4$, i.e.

$$\frac{((b+\beta)(c+\gamma)(d+\mu) - \mu\gamma\beta)(b+c+d+\beta+\gamma+\mu+a') + \alpha_1\alpha_2 aN_0(d+\mu)}{a'(b+\beta)(c+\gamma)(d+\mu)} > 1.$$

This shows that endemic disease equilibrium E_e is locally asymptotically stable, implying the validity of the assertion. □

1.1.6 Numerical simulation

With the help of numerical experiments, in recent decades, the development of epidemics of such diseases as HIV, smallpox (variola), malaria, acute respiratory viral infections (SARS), new influenza (H1N1) and, more recently, the SARS-COV-2 virus has been modeled, also using the SARS-COV- 2 based on the method of precedents [27].

Let us describe the numerical simulation of the malaria epidemic model using the Matlab program. The values of the model parameters are chosen arbitrarily. As already noted, a person infected with the malaria virus through an infectious mosquito bite is contagious only during a period of vulnerability, which lasts for several days.

Here are the values of parameters used for numerical simulation in Fig.1.2:

Table 1.1: Parameters for the simulation, which results are presented in Fig. 1.2.

α_1	α_2	β	γ	μ	a	a'	b	c	d	t_{max}	R_0
In Fig. 1.2, a											
0.8	0.9	0.3	0.4	0.01	0.8	0.01	0.2	0.4	0.01	60	0.54
In Fig. 1.2, b											
0.8	0.9	0.5	0.15	0.01	0.8	0.01	0.05	0.15	0.01	60	2.18

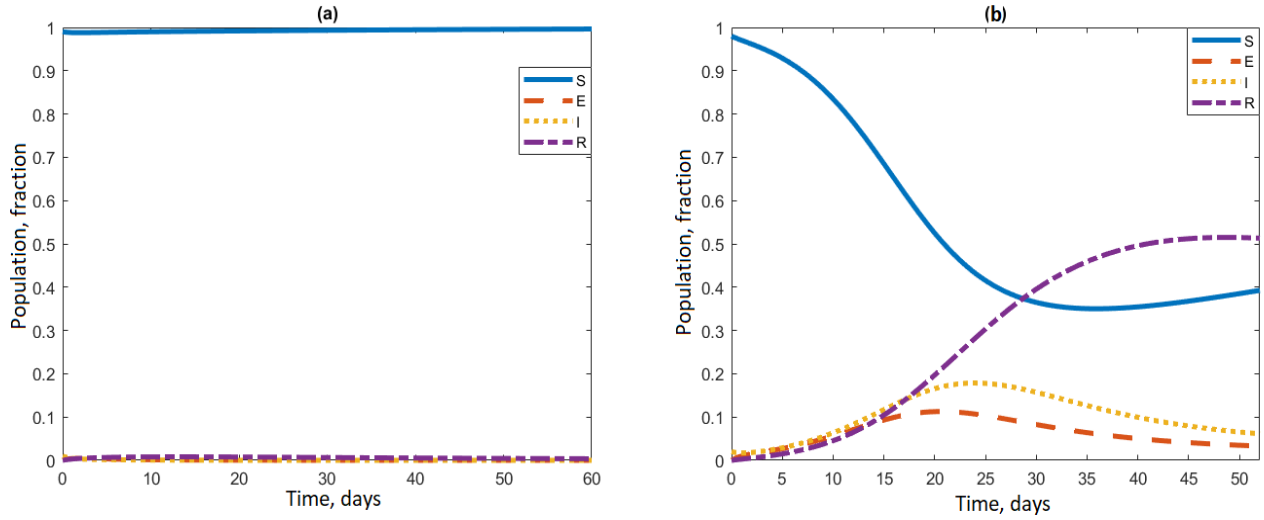

Figure 1.2: Development of the epidemic process at $R_0 \leq 1$ (a) and $R_0 \geq 1$ (b).

In Fig. 1.2 (a) when $R_0 < 1$, a disease is observed in a population with a lower risk, since the behavior of the curves corresponding to subpopulations is close to linear, the disease will eventually disappear in the population. In Fig.1.2 (b) for

$R_0 > 1$, it can be seen that the infected subpopulation I is rapidly increasing in comparison with the subpopulation bitten by the mosquito, but it is not yet affected by subpopulation E. In this state, the epidemic develops rapidly, and the entire population is at risk of becoming infected. Since malaria does not last long, most of the population tends to recover.

To eliminate this disease, we propose to use vaccination as an effective means of changing the dynamics of subpopulations. The purpose of vaccination is to immunize the population. It is worth noting that there is currently no highly effective malaria vaccine. Existing vaccines are $35 - 50\%$ effective and protect a person for several months. This should be taken into account when choosing the parameters that determine vaccination. The epidemic model of malaria in the presence of vaccination will be discussed in the next paragraph.

1.2 Malaria model with vaccination

In this section, we investigate the spread of malaria in a human population where mosquito population is introduced as a model parameter and human population has been vaccinated to get rid of this disease.

1.2.1 An epidemic model of malaria with vaccination

A diagram illustrating the spread of malaria in a population receiving a malaria vaccine is shown in Fig. 1.3. It is assumed that there are two populations, *host* (human population) and *vector* (mosquito population), but only human population is considered in the work where mosquito population is taken into account as a model parameter. In the presented model, vaccination is carried out among susceptible part of the population. To account for vaccination, the dv parameter equal to a percentage of vaccinated individuals in the population is introduced into the model. The population is assumed to be open.

The following notations are used in the model:

- $N(t)$ — size of human population;
- $S(t)$ — size of subpopulation of susceptible individuals;
- $E(t)$ — size of subpopulation of exposed people;
- $I(t)$ — size of subpopulation of infected people;

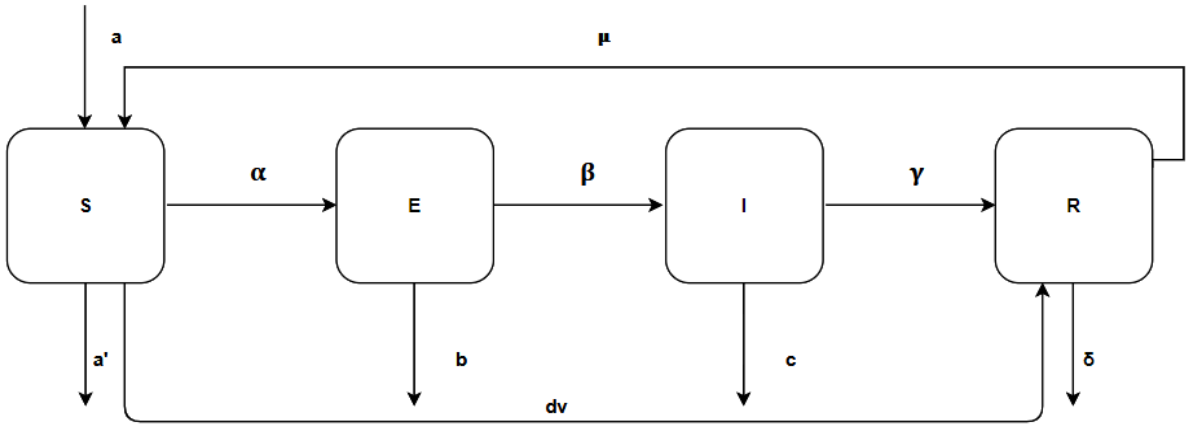

Figure 1.3: $SEIR$ model of malaria with vaccination

- $R(t)$ — size of subpopulation of recovered people;
- a — birth rate in human population;
- a' — mortality rate in subpopulation S;
- b — mortality rate in subpopulation E;
- c — mortality rate in infected subpopulation I;
- δ — mortality rate in recovered subpopulation R;
- α_1 — intensity of bites per person by one mosquito (defined as the number of bites per unit of time);
- α_2 — activity coefficient of contagiousness of malaria-infected mosquitoes;
- β — the intensity of people's transition from subpopulation E to I with the onset of disease symptoms;
- γ — the intensity of people's recovery, i.e. their transition from subpopulation I to R;
- μ — transition rate of people from recovered to susceptible subpopulation;
- $dv \in (0, 1)$ — vaccination rate of susceptible part of population.

A mathematical model of dynamics of subpopulations with vaccination can be

represented analytically by the following system of ordinary differential equations:

$$\begin{cases} \frac{dS(t)}{dt} = -\alpha I(t)S(t) + aN_0 + \mu R(t) - a'S(t) - dvS(t), \\ \frac{dE(t)}{dt} = \alpha I(t)S(t) - bE(t) - \beta E(t), \\ \frac{dI(t)}{dt} = \beta E(t) - cI(t) - \gamma I(t), \\ \frac{dR(t)}{dt} = \gamma I(t) + dvS(t) - \delta R(t) - \mu R(t), \end{cases} \tag{1.7}$$

where $\alpha = \frac{\alpha_1 \alpha_2}{N_0}$.

Note that vaccination is taken into account through the term $dvS(t)$, which is present in the right parts of the first and fourth equations with minus and plus signs, respectively. It is assumed that parameter dv does not change in time. In this chapter, the impact of this parameter on the epidemic development is demonstrated using numerical simulations in Section 1.2.4.

The initial conditions for the system of equations (1.7) are:

$$S(0) \geq 0, \quad E(0) \geq 0, \quad I(0) \geq 0, \quad R(0) \geq 0. \tag{1.8}$$

Therefore, the initial condition for the total population size is $N(0) = N_0 = S(0) + E(0) + I(0) + R(0) \geq 0$.

1.2.2 Equilibrium points

In this section, we will study two equilibrium points, namely, a disease-free equilibrium and an endemic equilibrium of the dynamical system described by the equations (1.7) with initial conditions (1.8).

To determine the equilibrium points of system (1.7) we solve the following system:

$$\begin{cases} -\alpha I(t)S(t) + aN_0 + \mu R(t) - a'S(t) - dvS(t) = 0, \\ \alpha I(t)S(t) - bE(t) - \beta E(t) = 0, \\ \beta E(t) - cI(t) - \gamma I(t) = 0, \\ \gamma I(t) + dvS(t) - \delta R(t) - \mu R(t) = 0. \end{cases}$$

Consider two solutions to this system (equilibrium points interesting for us):

1. Equilibrium point without disease $E_s = (N_0, 0, 0, 0)$;

2. Equilibrium point $E_e = (S^*, E^*, I^*, R^*)$, where

$$\begin{aligned} S^* &= \frac{(b+\beta)(c+\gamma)}{\alpha_1\alpha_2\beta}, \\ E^* &= \frac{c+\gamma}{\beta}I^*, \\ I^* &= \frac{(b+\beta)(c+\gamma)((\delta+\mu)(aN_0-a')-\delta dv)}{\alpha_1\alpha_2((b+\beta)(c+\gamma)(\delta+\mu)-\mu\gamma\beta)}, \\ R^* &= \frac{\gamma}{\delta+\mu}I^* + \frac{dv}{\delta+\mu}S^*. \end{aligned}$$

The point E_e is called an endemic equilibrium point, at which there is a nonzero part of susceptible, exposed, infected and recovered population. The speed of recovery depends on the severity of the disease and the methods used to eliminate the disease.

Remark 1.1. *The way of calculating basic reproductive number R_0 is described in paper* [3]. *In this work, R_0 remains unchanged compared to R_0 and this number is equal to*

$$R_0 = \frac{\alpha_1\alpha_2\beta}{(b+\beta)(c+\gamma)}. \tag{1.9}$$

1.2.3 Study of stability of equilibria

Local stability of equilibrium without disease

In this section, conditions for the stability of equilibrium points in the epidemic model with vaccination are obtained.

Proposition 1.4. *If $R_0 < 1$, then disease-free equilibrium $E_s = (N_0, 0, 0, 0)$ is locally asymptotically stable.*

Proof. The Jacobi matrix corresponding to system (1.7) has the form:

$$J(S,E,I,R) = \begin{pmatrix} -\frac{\alpha_1\alpha_2}{N_0}I - a' - dv & 0 & -\frac{\alpha_1\alpha_2}{N_0}S & \mu \\ \frac{\alpha_1\alpha_2}{N_0}I & -b-\beta & \frac{\alpha_1\alpha_2}{N_0}S & 0 \\ 0 & \beta & -c-\gamma & 0 \\ dv & 0 & \gamma & -\delta-\mu \end{pmatrix}.$$

The Jacobi matrix at point E_s is equal to

$$J(E_s) = \begin{pmatrix} -a'-dv & 0 & -\alpha_1\alpha_2 & \mu \\ 0 & -b-\beta & \alpha_1\alpha_2 & 0 \\ 0 & \beta & -c-\gamma & 0 \\ dv & 0 & \gamma & -\delta-\mu \end{pmatrix}.$$

Let us find the eigenvalues of matrix $J(E_s)$, equating its determinant to zero, we obtain the equation

$$\lambda^4 + B_1\lambda^3 + B_2\lambda^2 + B_3\lambda + B_4 = 0,$$

where

$$\begin{aligned}
B_1 &= a' + \delta + \mu + dv + \beta + b + c + \gamma,\\
B_2 &= (a' + dv)(\delta + \mu) + dv\mu + (b + \beta)(c + \gamma) -\\
&\quad - \beta\alpha_1\alpha_2 + (a' + dv + \delta + \mu)(b + \beta + c + \gamma),\\
B_3 &= (a' + dv + \delta + \mu)[(b + \beta)(c + \gamma) - \beta\alpha_1\alpha_2] +\\
&\quad + [(a' + dv)(\delta + \mu) + dv\mu](b + \beta + c + \gamma),\\
B_4 &= [(a' + dv)(\delta + \mu) + dv\mu][(b + \beta)(c + \gamma) - \beta\alpha_1\alpha_2] + \mu dv.
\end{aligned}$$

The characteristic equation has four solutions, which are eigenvalues of matrix $J(E_s)$. The Routh-Hurwitz criterion is as follows. For dynamic system (1.7) to be stable, it is necessary and sufficient that all the main diagonal minors of the Hurwitz determinant should be positive, provided that the coefficient at the highest degree in a characteristic equation is positive. We use this criterion, for which we write an auxiliary matrix

$$\begin{vmatrix}
1 & B_2 & B_4 & 0 & 0\\
B_1 & B_3 & 0 & 0 & 0\\
\dfrac{B_1B_2 - B_3}{B_1} & B_4 & 0 & 0 & 0\\
\dfrac{B_3(B_1B_2 - B_3) - B_1^2B_4}{B_1B_2 - B_3} & 0 & 0 & 0 & 0\\
B_4 & 0 & 0 & 0 & 0
\end{vmatrix}.$$

Applying the Routh-Hurwitz criterion, we obtain that system (1.7) is asymptotically stable at equilibrium point E_s if the following inequalities are true:

$$\begin{aligned}
B_1 &> 0,\\
\frac{B_1B_2 - B_3}{B_1} &> 0,\\
\frac{B_3(B_1B_2 - B_3) - B_1^2B_4}{B_1B_2 - B_3} &> 0,\\
B_4 &> 0,
\end{aligned}$$

which is equivalent to the system

$$\begin{aligned} B_1 > 0, \\ B_1B_2 - B_3 > 0, \\ B_3(B_1B_2 - B_3) - B_1^2B_4 > 0, \\ B_4 > 0. \end{aligned}$$

Let us verify the validity of these inequalities under the condition that $R_0 < 1$. Inequality $R_0 < 1$ is equivalent to inequality $(b+\beta)(c+\gamma) - \alpha_1\alpha_2\beta > 0$. It is obvious that $B_1 > 0$. It follows from condition $R_0 < 1$ that $B_4 > 0$. Substituting the expressions for B_1, B_2 and B_3 into expression $B_1B_2 - B_3$, after simple algebraic transformations we get that $B_1B_2 - B_3 > 0$ for $R_0 < 1$. Similarly, we obtain that $B_3(B_1B_2 - B_3) - B_1^2B_4 > 0$ for $R_0 < 1$. Algebraic calculations were made using the Matlab program. The assertion has been proven. □

Local stability of endemic equilibrium E_e

Proposition 1.5. *If* $R_0 > 1$ *and* $dv < \frac{1}{\delta}(\delta+\mu)(aN_0 - a')$*, then endemic equilibrium point* $E_e = (S^*, E^*, I^*, R^*)$ *is locally asymptotically stable.*

Proof. The Jacobi matrix corresponding to system (1.7) has the form:

$$J(S,E,I,R) = \begin{pmatrix} -\frac{\alpha_1\alpha_2}{N_0}I - a' - dv & 0 & -\frac{\alpha_1\alpha_2}{N_0}S & \mu \\ \frac{\alpha_1\alpha_2}{N_0}I & -b-\beta & \frac{\alpha_1\alpha_2}{N_0}I & 0 \\ 0 & \beta & -c-\gamma & 0 \\ dv & 0 & \gamma & -\delta-\mu \end{pmatrix}.$$

The Jacobi matrix at point $E_e = (S^*, E^*, I^*, R^*)$ is equal to

$$J(E_e) = \begin{pmatrix} -\alpha_1\alpha_2\frac{I^*}{N_0} - a' - dv & 0 & -\alpha_1\alpha_2\frac{S^*}{N_0} & \mu \\ \alpha_1\alpha_2\frac{I^*}{N_0} & -b-\beta & \alpha_1\alpha_2\frac{S^*}{N_0} & 0 \\ 0 & \beta & -c-\gamma & 0 \\ dv & 0 & \gamma & -\delta-\mu \end{pmatrix}.$$

Let us determine the eigenvalues of this matrix $J(E_e)$. Equating its determinant to zero, we obtain the equation:

$$\lambda^4 + C_1\lambda^3 + C_2\lambda^2 + C_3\lambda + C_4 = 0,$$

where

$$
\begin{aligned}
C_1 &= b + c + \delta + \beta + \gamma + \mu + a' + \frac{\alpha_1\alpha_2}{N_0} I^*, \\
C_2 &= (a' + \frac{\alpha_1\alpha_2}{N_0} I^*)(\delta + \mu) + b + \beta + c + \gamma + \\
&\quad + (a' + \delta + \mu + \frac{\alpha_1\alpha_2}{N_0} I^*)(b + c + \beta + \gamma) - \frac{\alpha_1\alpha_2}{N_0} S^*, \\
C_3 &= (a' + \frac{\alpha_1\alpha_2}{N_0} I^*)(\delta + \mu)(b + c + \beta + \gamma) + \\
&\quad + (b + \beta)(c + \gamma)(a' + \delta + \mu + \frac{\alpha_1\alpha_2}{N_0} I^*) - \frac{\beta\alpha_1\alpha_2}{N_0} S^*, \\
C_4 &= (b + \beta)(c + \gamma)(\delta + \mu)(a' + \frac{\alpha_1\alpha_2}{N_0} I^*) + \\
&\quad + \frac{\beta\mu\alpha_1\alpha_2}{N_0}(dvS^* + \gamma I^*) - \frac{\alpha_1\alpha_2\beta a'(\delta + \mu)}{N_0} S^*.
\end{aligned}
$$

The characteristic equation has four solutions, which are eigenvalues of matrix $J(E_e)$.

We use the Routh-Hurwitz criterion to study stability of the system at point E_e. To do this, we write an auxiliary matrix (the Routh-Hurwitz matrix):

$$
\begin{vmatrix}
1 & C_2 & C_4 & 0 & 0 \\
C_1 & C_3 & 0 & 0 & 0 \\
\dfrac{C_1C_2 - C_3}{C_1} & C_4 & 0 & 0 & 0 \\
\dfrac{C_3(C_1C_2 - C_3) - C_1^2C_4}{C_1C_2 - C_3} & 0 & 0 & 0 & 0 \\
C_4 & 0 & 0 & 0 & 0
\end{vmatrix}
$$

Applying the Routh-Hurwitz criterion, we obtain that system (1.7) is asymptotically stable at equilibrium point E_e if the following inequalities hold:

$$
\begin{aligned}
C_1 &> 0, \\
\frac{C_1C_2 - C_3}{C_1} &> 0, \\
\frac{C_3(C_1C_2 - C_3) - C_1^2C_4}{C_1C_2 - C_3} &> 0, \\
C_4 &> 0,
\end{aligned}
$$

which is equivalent to the system

$$\begin{aligned} C_1 &> 0, \\ C_4 &> 0, \\ C_1C_2 - C_3 &> 0, \\ C_3(C_1C_2 - C_3) - C_1^2C_4 &> 0. \end{aligned}$$

Let us check the validity of these inequalities under the condition that $R_0 > 1$ and $dv < \frac{1}{\delta}(\delta + \mu)(aN_0 - a')$. It is obvious that $C_1 > 0$ if $I^* > 0$, the last inequality holds for $dv < \frac{1}{\delta}(\delta + \mu)(aN_0 - a')$. It follows from condition $R_0 > 1$ that $S^* < 1$. Substituting the expressions S^*, I^*, R^* and E^* into C_1, C_2, C_3 and C_4, after simple algebraic transformations, we obtain that the last system of inequalities is satisfied. Algebraic calculations were made using the Matlab program. The assertion has been proven. □

1.2.4 Numerical simulation

This section describes the results of a numerical simulation that takes into account the vaccination of the population as a way to control malaria. The simulation was carried out using the Matlab program. The parameters for which numerical simulations with vaccination were carried out are shown in the following table:

Table 1.2: The parameters for simulation, which results are presented in Fig. 1.4 and Fig. 1.5

α_1	α_2	β	γ	μ	a	a'	b	c	δ	t_{max}	R_0
In Fig. 1.4											
0.8	0.9	0.3	0.4	0.01	0.8	0.01	0.2	0.4	0.01	60	0.54
In Fig. 1.5											
0.8	0.9	0.5	0.15	0.01	0.8	0.01	0.05	0.15	0.01	60	2.18

Particular attention is paid to studying the influence of the values of dv parameter characterizing a vaccination level of population, on the nature of epidemic development. The following values of dv parameter are considered: 0.00, 0.03, 0.08, 0.15, 0.25, 0.50 for two sets of other parameters presented in the above table, with different values of R_0: 0.54 for the first data set and 2.18 for the second set. The value of R_0 is calculated using formula (1.9) for each data set.

Fig. 1.4 presents the results of numerical simulation of population dynamics for the first data set, for which $R_0 < 1$. If you look at graph a_1, you can see

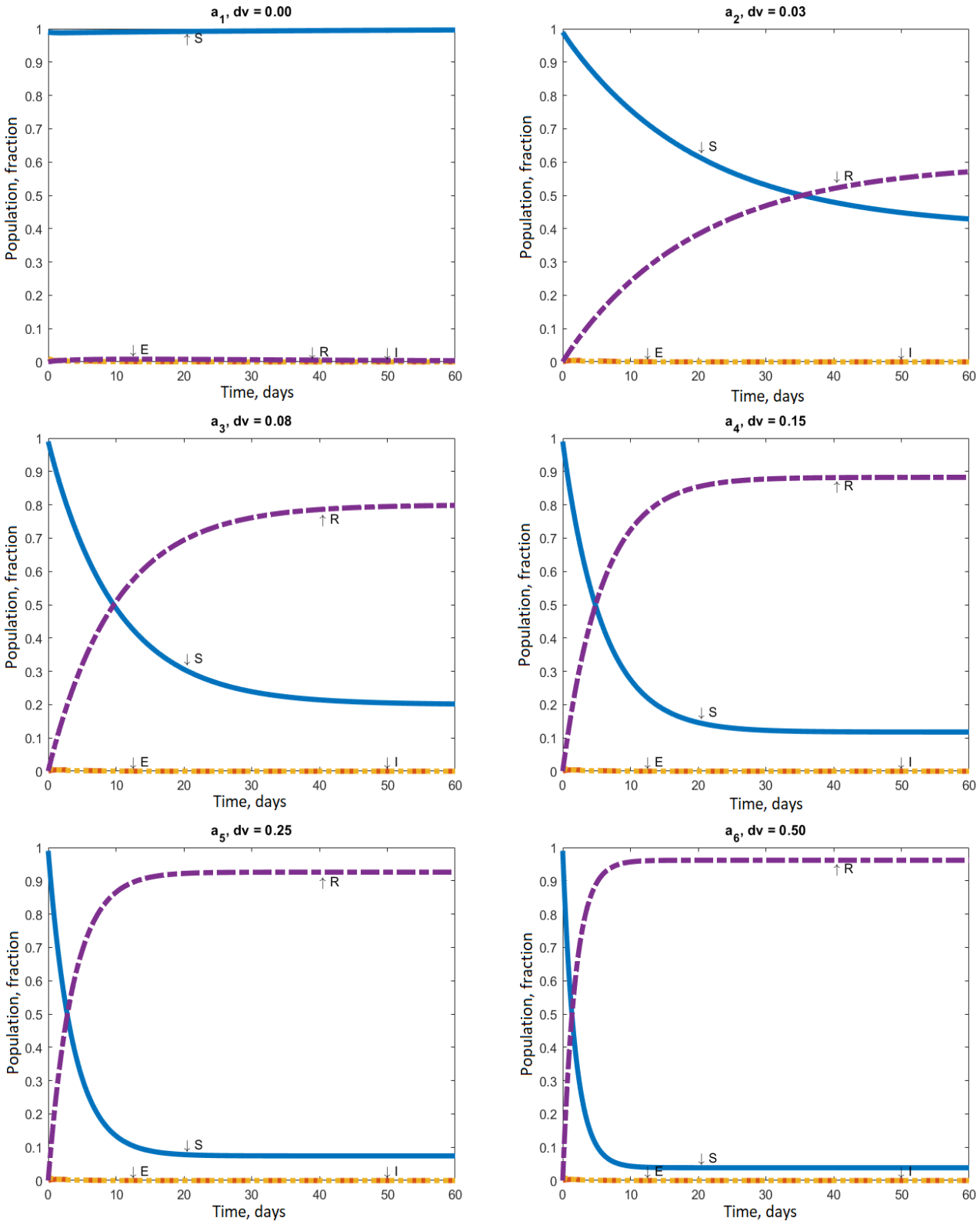

Figure 1.4: Epidemic process for $R_0 < 1$ for different values of dv.

that the disease is practically absent, and the behavior of the curves showing the dynamics of subpopulations is close to linear, which indicates the stability of the population composition. In Fig. 1.4 (a_2, a_3), with a low percentage of population vaccination (3% and 8%), a subpopulation curve $R(t)$ of recovering people has an

exponential growth, a curve of subpopulation of susceptible people tends to gradual decrease, i.e. the susceptible move into the recovered group, and a curve of infected subpopulation $I(t)$ is almost zero, i.e. the disease completely disappears from the population. In Fig. 1.4 (a_4, a_5, a_6) with an increase in the percentage of vaccinated population (15%, 25% and 50%), a subpopulation curve for recovered people rapidly grows and becomes close to linear at a certain time. A susceptible subpopulation curve decreases rapidly before becoming linear, and an infected subpopulation curve $I(t)$ is practically zero, in other words, the disease completely disappears from the population.

Consider the second data set, for which $R_0 > 1$. From Fig. 1.5 (b_1) it can be seen that the disease is present in population and the curves corresponding to subpopulations are nonmonotonic, $S(t)$ first decreases, then increases, while $R(t)$, $E(t)$ and $I(t)$ first increase, then decrease. In Fig. 1.5 (b_2 and b_3) with a low percentage of population vaccination (3% and 8% respectively), a recovering subpopulation curve $R(t)$ grows almost exponentially, susceptible subpopulation $S(t)$ rapidly decreases and passes into a group of recovered people $R(t)$ due to vaccination, while subpopulation of infected people $I(t)$ at some point in time becomes linear, that is, the disease gradually disappears from the population due to the population vaccination. In Fig. 1.5 (b_4, b_5 and b_6) with a high percentage of vaccinated population (15%, 25% and 50% respectively), the subpopulation curve of recovered patients $R(t)$ increases rapidly and at some point becomes close to linear. A curve of susceptible subpopulation $S(t)$ decreases rapidly and also becomes close to a linear function, and curve of infected subpopulation $I(t)$ is almost zero over the entire time interval, which indicates a complete disappearance of the disease in the population.

Numerical modeling clearly demonstrates that vaccination plays an important part in ensuring population resistance to disease and preventing the epidemic development. Although there is no highly effective malaria vaccine, it seems essential to vaccinate the population with available vaccines, as well as to recommend the use of other malaria prevention measures (drugs, impregnated mosquito nets, etc.) to reduce the values of the parameters that characterize the rate of disease transmission.

Now we study the effect of vaccination on human population at various levels of virus infection. The level of infection is described using R_0, which is the number of base reproductions, the value of which is obtained using the parameters given in the

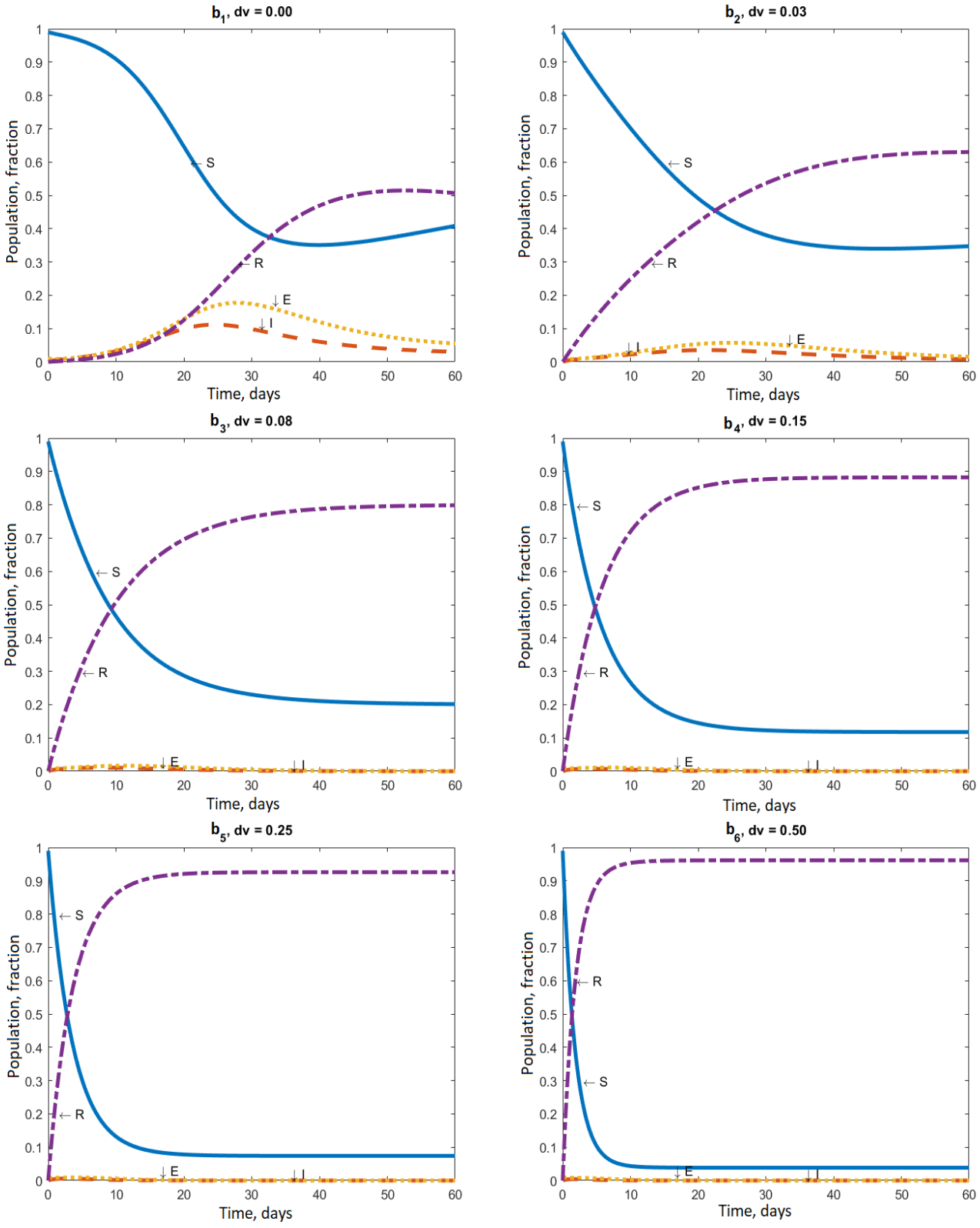

Figure 1.5: Epidemic process for $R_0 > 1$ and for different values of dv.

tables below. For each R_0 value, we will apply different vaccination rate values. We use the following dv values: 0.08, 0.25, 0.75 for different values of R_0: 0.72, 2.5, 3 and 5. The value of R_0 is calculated using formula (1.9) for each data set found in the tables below.

Table 1.3: Parameters for the simulation, which results are presented in Fig. 1.6.

α_1	α_2	β	γ	μ	a	a'	b	c	δ	t_{max}	R_0
In Fig. 1.6											
0.8	0.9	0.3	0.2	0.01	0.8	0.01	0.2	0.4	0.01	60	0.72

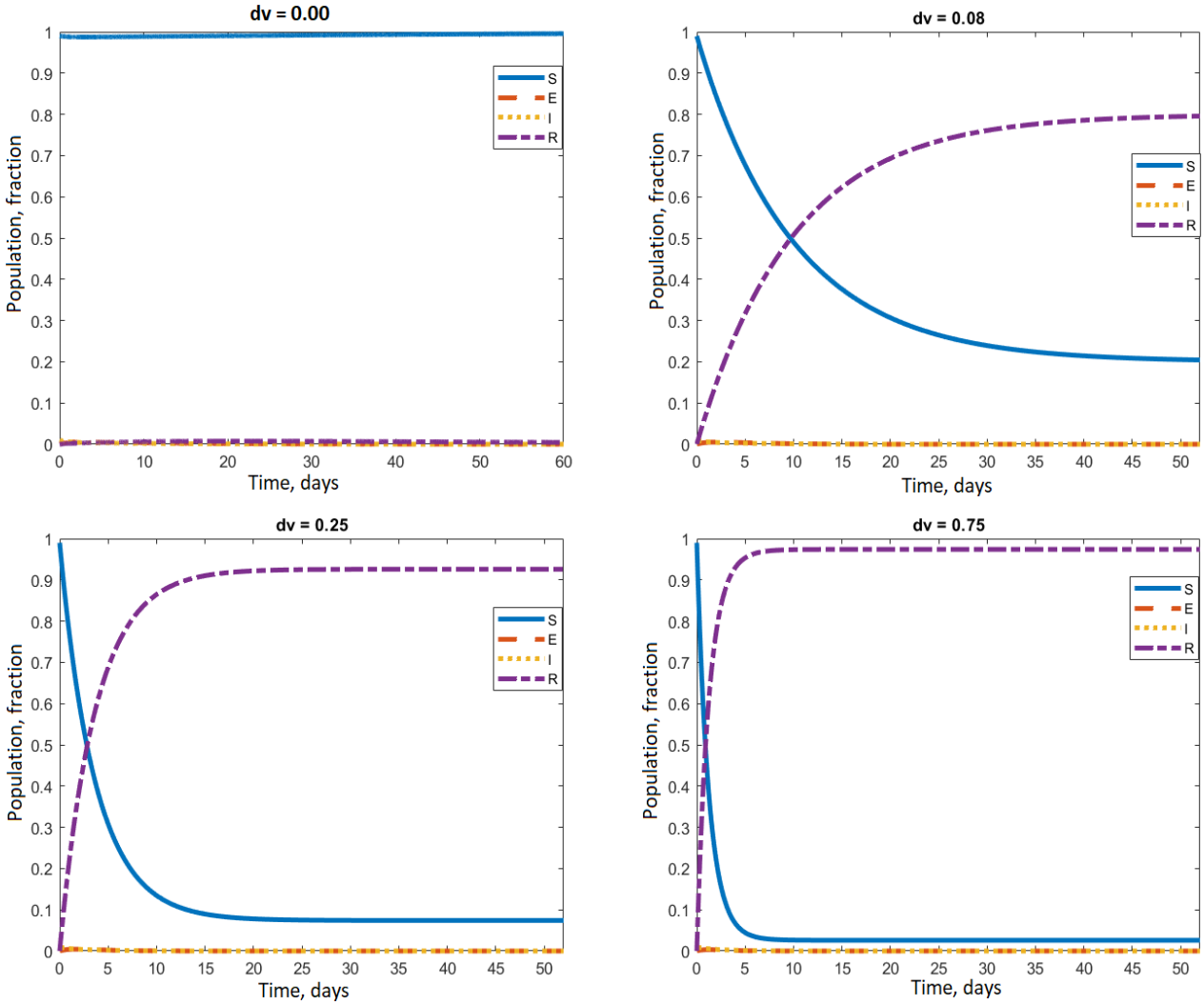

Figure 1.6: Epidemic process with $R_0 = 0.72$ for different values of dv.

When using the data from Table 1.3, for which $R_0 = 0.72$, it can be seen that the disease is practically absent on the first graph, and the behavior of the curves showing the dynamics of subpopulations is close to linear, which indicates the stability of the population composition, i.e. the disease will disappear after a while. At a population vaccination rate of 8%, we find that susceptible population $(S(t))$ transforms rapidly into the recovered population $(R(t))$, and the curves clearly show that susceptible population rapidly decreases while the curve representing recovered population grows exponentially. At a vaccination level of 25%, there is a very rapid growth of recovered population $(R(t))$. A recovered population curve grows

exponentially until reaching a stationary value. On the other hand, susceptible population ($S(t)$) is a curve that decreases exponentially until reaching a stationary value. At a vaccination level of 75%, a recovered population curve ($R(t)$) reaches a practically constant value in less than 5 days, and a susceptible population curve ($S(t)$) has a similar behavior, but it decreases to the minimum values, and then remains constant. The disease is practically absent as a transmission rate of R_0 is low and a person infected and able to transmit the virus can infect on average less than one person. The representative curves for exposed population ($E(t)$) and infected population ($I(t)$) are close to linear.

Table 1.4: Parameters for the simulation, which results are presented in Fig. 1.7.

α_1	α_2	β	γ	μ	a	a'	b	c	δ	t_{max}	R_0
In Fig. 1.7											
0.9	0.9	0.66	0.15	0.01	0.8	0.01	0.05	0.15	0.01	60	2.5

Consider the data from Table 1.4 for which $R_0 = 2.5$. We can notice that in the first graph a curve of infected population ($I(t)$) rises rapidly until the 20th day, when the epidemic peak is reached, and without measures of influencing disease, it can be dangerous for the population. It can be seen that a susceptible population curve ($S(t)$) decreases rapidly, and an exposed population curve ($E(t)$) is below an infected population curve ($I(t)$), which explains gradual disappearance of exposed subpopulation. Since malaria does not last long, after three weeks a representative curve of infected population ($I(t)$) begins to decrease. With a population vaccination rate of 8%, we find that susceptible population ($S(t)$) rapidly transforms into recovered population ($R(t)$), and that the plots clearly show that a susceptible population curve decreases rapidly, while a representative curve of recovered population increases exponentially. Although the disease still exists in population, as an infected population curve ($I(t)$) shows, but it is not a big threat as population tends to quick recovery by vaccinating population. At a vaccination rate of 25%, we see a very rapid rise of a recovered population curve ($R(t)$). A recovered population curve increases exponentially before becoming constant, on the other hand, susceptible subpopulation ($S(t)$) decreases exponentially before becoming stationary. At a higher vaccination rate of 75%, a recovered population curve ($R(t)$) rises and quickly becomes stationary over a very short period of time, while a susceptible population curve ($S(t)$) decreases very rapidly before becoming linear. A transmission rate of

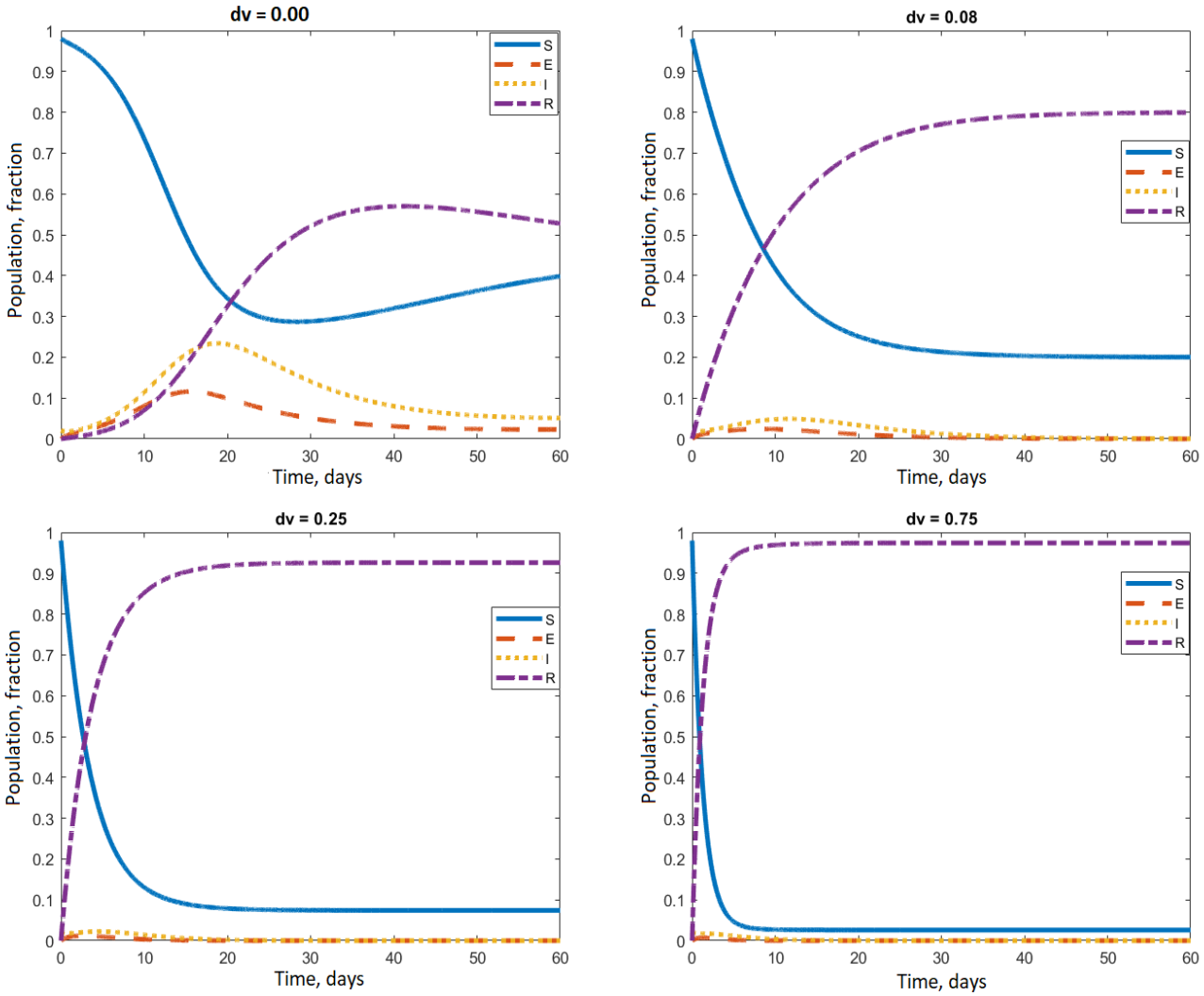

Figure 1.7: Epidemic process with $R_0 = 2.5$ for different values of dv.

R_0 is important because one infected person who can transmit the virus can infect on average more than two people. Using a vaccine helps reduce damage that the disease can cause.

Table 1.5: Parameters for the simulation, which results are presented in Fig. 1.8.

α_1	α_2	β	γ	μ	a	a'	b	c	δ	t_{max}	R_0
In Fig. 1.8											
0.9	0.9	0.6	0.15	0.02	0.8	0.01	0.2	0.05	0.01	60	3.04

Consider the data from Table 1.5 for which $R_0 = 3.04$. It can be seen that in the first graph, an infected subpopulation curve $(I(t))$ rises rapidly until the 21st day, when the epidemic reaches its peak, and it can be life-threatening without measures to control the disease. A susceptible subpopulation curve $(S(t))$ decreases, and an exposed subpopulation curve $(E(t))$ is below the infected subpopulation curve $(I(t))$

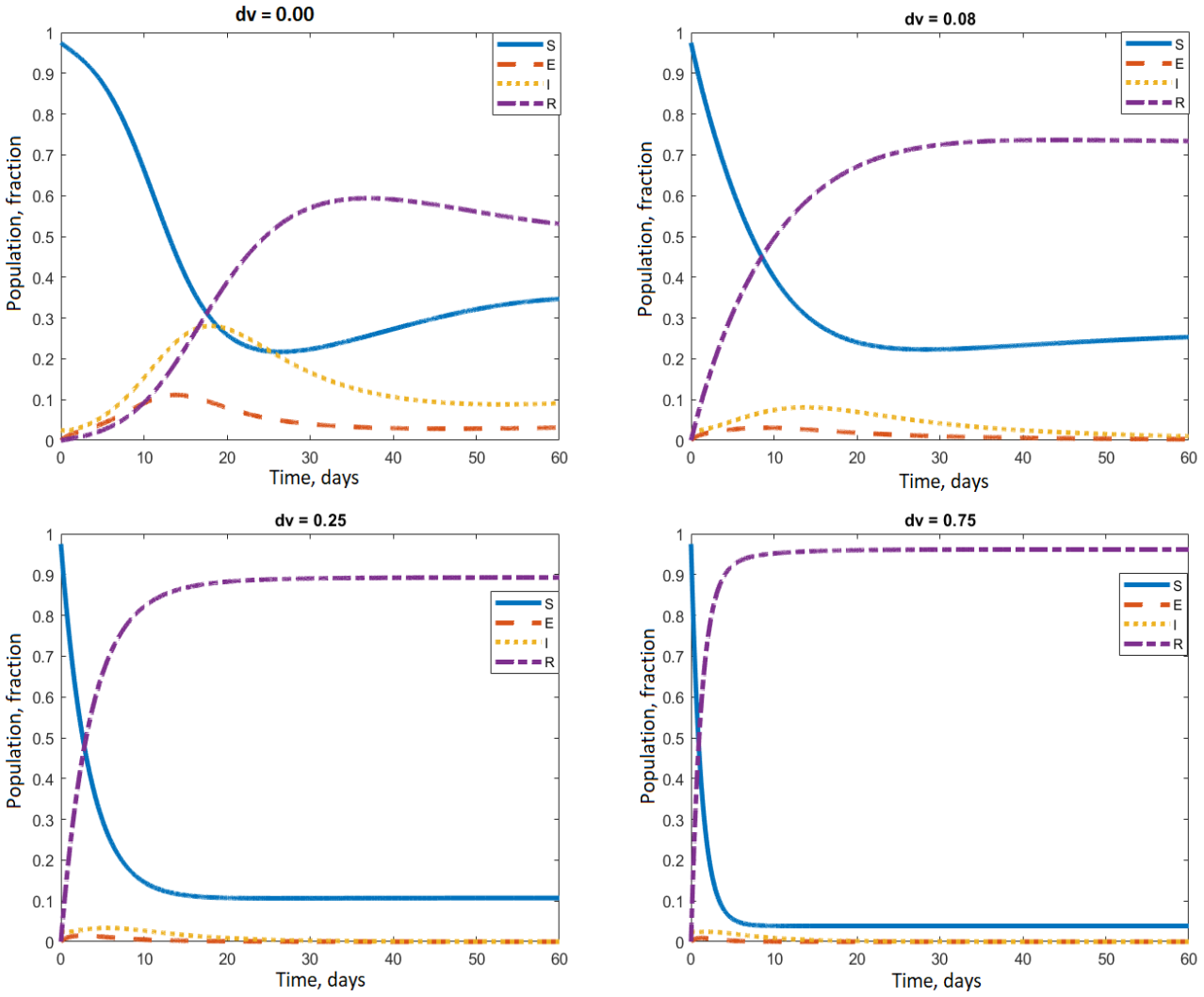

Figure 1.8: Epidemic process with $R_0 = 3.04$ for different values of dv.

which becomes close to linear after some time (30th day), which explains gradual disappearance of the bitten subpopulation. Since malaria does not last long, a representative curve of infected subpopulation $(I(t))$ begins to decrease by the end of the 25th day. At a vaccination rate of 8%, we find that susceptible subpopulation $(S(t))$ gradually transforms into recovered subpopulation $(R(t))$, and the curves clearly show that a susceptible population curve gradually begins to decrease while a representative curve of recovered population increases rapidly. Although the disease still exists in population, as shown by an infected population curve $(I(t))$, but the epidemic peak is reached earlier this time (on the 15th day) due to more active vaccination. Then population tends to gradual recovery. At a higher vaccination rate of 25%, we see a very rapid increase of a recovered-population curve $(R(t))$. A recovered population curve increases rapidly before becoming stationary at the end of a certain period, on the other hand, susceptible population $(S(t))$ gradu-

ally decreases before becoming stationary, also after a certain time (30th day) an infected population curve has the appearance of a bell before becoming linear. At a higher vaccination level of 75%, a recovered population curve ($R(t)$) rises and quickly becomes stationary by the end of the 5th day, and a susceptible population curve ($S(t)$) decreases very quickly before becoming linear. The disease exists and a transmission rate of R_0 is significant, but more frequent vaccination reduces prevalence of the disease in the population.

Table 1.6: Parameters for the simulation, which results are presented in Fig. 1.9.

α_1	α_2	β	γ	μ	a	a'	b	c	δ	t_{max}	R_0
In Fig. 1.9											
1.2	0.8	0.8	0.1	0.01	0.6	0.01	0.21	0.05	0.01	60	5.07

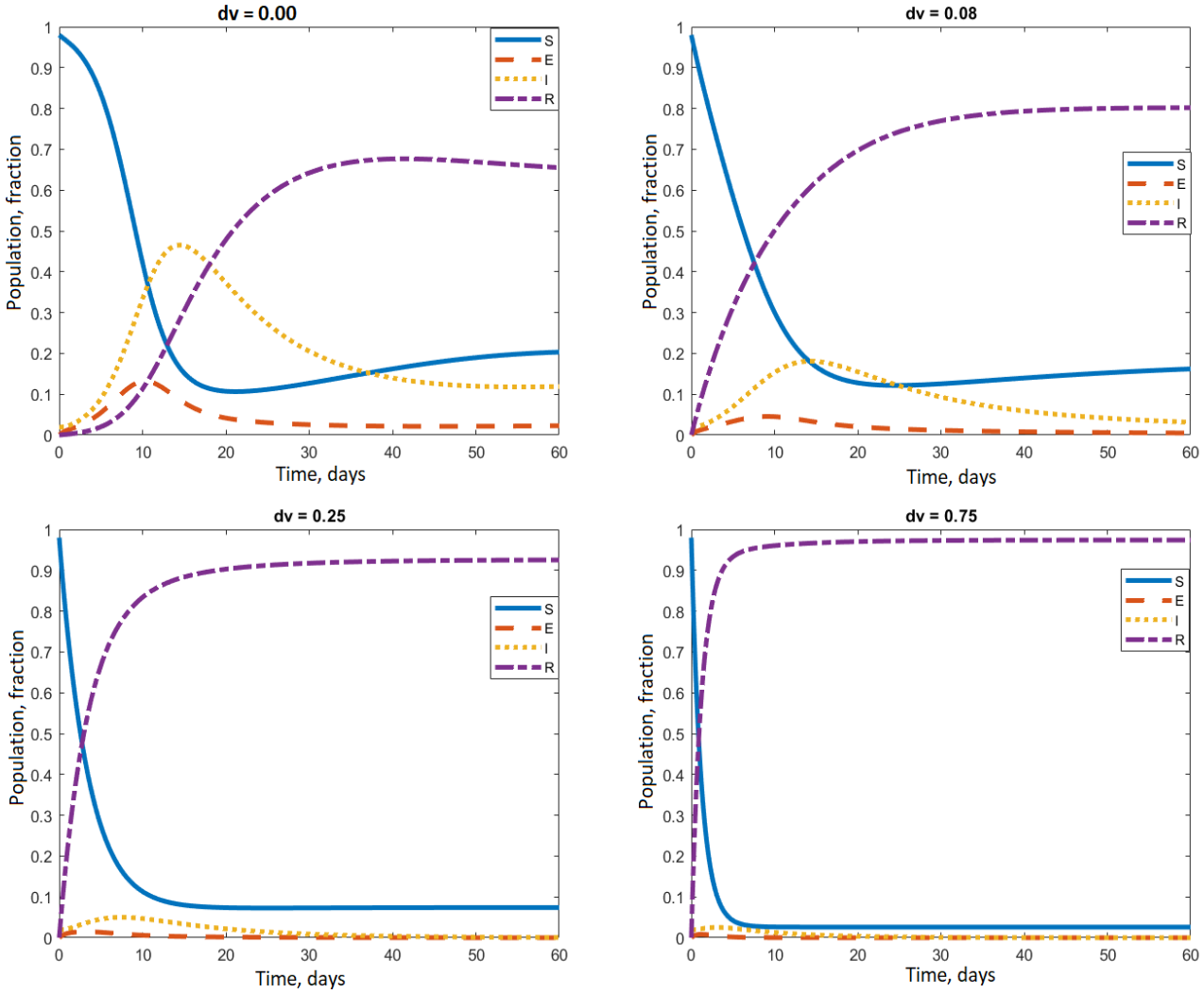

Figure 1.9: Epidemic process with $R_0 = 5.07$ for different values of dv.

Consider the data from Table 1.6 for which $R_0 = 5.07$. We can notice that in

the first graph an infected population curve ($I(t)$) grows exponentially and will take values greater than the values of all other curves by the 15th day of reaching the epidemic peak. In this case, one infected person can infect on average more than 5 people. We see that a susceptible population curve ($S(t)$) decreases exponentially, and an exposed population curve ($E(t)$) becomes linear by the end of the 20th day, which explains almost total disappearance of exposed population and its transformation into fully infected if the population is not vaccinated. Starting with the 17th day, a representative curve of infected population ($I(t)$) decreases as malaria does not last long. It should be noted that the nature of changing dynamics of subpopulations is similar to the previous results, but it is worth noting that a rate of transmission of the disease has a significant impact on the duration of the epidemic. The larger number R_0, the higher level of vaccination is required to eliminate the disease in the population.

1.3 Conclusion to Chapter 1

The first chapter presents two mathematical models: without vaccination and with vaccination of the malaria epidemic based on the $SEIR$ model and its modifications. The models take into account a transition factor from the recovered to the susceptible population (occurs in the case of malaria and it is confirmed by medical research, but not usually used in the $SEIR$ model). The proposed models of the malaria epidemic are described by systems of ordinary differential equations with positive initial conditions. It is shown that the mathematical models defined in this way are in the region Ω. For each model, the basic reproductive number R_0 is found characterizing the nature of the dynamics of malaria transmission, namely, stationary states (equilibrium points) of the epidemic process. Numerical modeling shows that the higher the level of vaccination of the population, the faster the epidemic can be "eliminated". Unfortunately, malaria is a disease for which vaccines have a low level of effectiveness, but vaccination of a significant part of the population can successfully cope with the epidemic.

Chapter 2

Vector epidemic model of malaria without and with vaccination

This chapter presents dynamic epidemic models of type vector-host with direct transmission between two populations [65]. The malaria distribution model is determined by a system of ordinary differential equations. The host (human) population is divided into four subpopulations: susceptible, exposed, infected and recovered, and the vector (mosquito) population is divided into three subpopulations: susceptible, exposed and infected. Using the theory of Lyapunov functions, sufficient conditions for the global stability of equilibrium without diseases and endemic equilibrium are determined. The basic reproductive number characterizing the evolution of the epidemic in the population has been found. Numerical modeling was carried out to study the influence of key parameters on the spread of vector-borne diseases.

A model of direct vector-to-host transmission with vaccination is also presented in this chapter. The dynamics of malaria spread is given by a system of ordinary differential equations. Unlike the previous model, it is assumed that the human population can be vaccinated. Numerical modeling was also carried out for this model to study the influence of key parameters on the spread of vector-borne diseases.

2.1 Model of a vector-borne malaria epidemic

2.1.1 Model $SEIRS_kE_kI_k$

We start with the description of model $SEIRS_kE_kI_k$ (also see [38]). Disease-transmitting mosquitoes can be in one of three states: susceptible (S_k),exposed (E_k), and infected (I_k). The bite of the female *Anopheles* mosquito carrying the malaria virus transfers a healthy (susceptible) person (S) into a category called in-

fected hosts (I). Uninfected population but at a high risk of contracting malaria is the susceptible population. People who recover from malaria through medical treatment without a threat to their lives get into a group of people (R) who have recovered. Figure 2.1 shows an interaction diagram between human population (host) and mosquito population (carrier or vector) for malaria transmission.

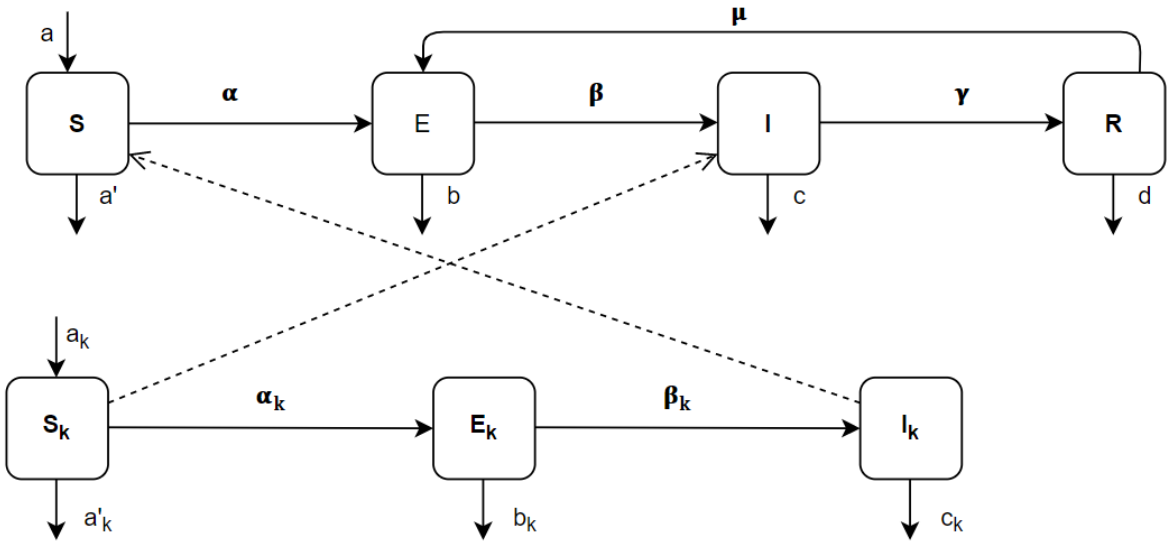

Figure 2.1: Malaria model

The size of the entire host population is $N(t) = S(t) + E(t) + I(t) + R(t)$, and the size of the vector population is $N_k(t) = S_k(t) + E_k(t) + I_k(t)$.

The mathematical model of population dynamics (human and mosquito) can be represented analytically by the following nonlinear system of seven ordinary differential equations:

$$\begin{cases} \dfrac{dS(t)}{dt} &= -\alpha S(t) I_k(t) + aN(t) - a'S(t), \\ \dfrac{dE(t)}{dt} &= \alpha S(t) I_k(t) + \mu R(t) - bE(t) - \beta E(t), \\ \dfrac{dI(t)}{dt} &= \beta E(t) - cI(t) - \gamma I(t), \\ \dfrac{dR(t)}{dt} &= \gamma I(t) - dR(t) - \mu R(t), \\ \dfrac{dS_k(t)}{dt} &= -\alpha_k S_k(t) I(t) + a_k N_k(t) - a'_k S_k(t), \\ \dfrac{dE_k(t)}{dt} &= \alpha_k S_k(t) I(t) - b_k E_k(t) - \beta_k E_k(t), \\ \dfrac{dI_k(t)}{dt} &= \beta_k E_k(t) - c_k I_k(t), \end{cases} \tag{2.1}$$

with initial conditions

$$S(0) \geq 0,\ E(0) \geq 0,\ I(0) \geq 0,\ R(0) \geq 0,\ S_k(0) \geq 0,\ E_k(0) \geq 0,\ I_k(0) \geq 0. \tag{2.2}$$

The general population dynamics is represented by equation:

$$\frac{dN}{dt} = aN_0 - a'S - bE - cI - dR.$$

The given initial conditions (2.2) must satisfy the inequality: $N(0) \geq 0$. Thus, the total population size $N(t)$ remains positive and bounded during the entire time $t > 0$. The dynamics of general population of carriers is as follows:

$$\frac{dN_k}{dt} = a_k N_{0_k} - a'_k S_k - b_k E_k - c_k I_k.$$

The model uses the following parameters:

- $N(t)$ — size of human population;
- $S(t)$ — size of subpopulation of susceptible individuals;
- $E(t)$ — size of subpopulation of exposed people (bitten by mosquito);
- $I(t)$ — size of subpopulation of infected people;
- $R(t)$ — size of subpopulation of recovered people;
- a — birth rate in human population;
- a' — mortality rate among subpopulation S;
- b — mortality rate among subpopulation E;
- c — mortality rate among infected subpopulation I;
- d — mortality rate among recovered subpopulation R;
- β — intensity of people's transition from subpopulation E to I, with the onset of disease symptoms;
- γ — intensity of people's recovery, i.e. transition from subpopulation I to R;
- μ — rate of people's return from recovered to susceptible;
- α — probability of transmitting infection through an infected mosquito bite to a susceptible person;

- $N_k(t)$ — total size of mosquito population;
- $S_k(t)$ — number of mosquitoes that can be infected;
- $E_k(t)$ — number of mosquitoes susceptible to the disease;
- $I_k(t)$ — number of infected mosquitoes;
- $a_k(t)$ — birth rate in mosquito population;
- $a'_k(t)$ — mortality in susceptible mosquito populations;
- $b_k(t)$ — mortality in exposed mosquito population;
- $c_k(t)$ — mortality in infected mosquito population;
- $\alpha_k(t)$ — probability of transition from a group of susceptible mosquitoes to a group of exposed ones;
- $\beta_k(t)$ — transition rate of mosquitoes from susceptible to exposed subpopulation.

2.1.2 Region of admissible values

A mathematical model represented by a system of differential equations (2.1) describes changes in human and mosquito populations. Therefore, it is important to make sure that all solutions with nonnegative initial conditions (2.2) always remain nonnegative. All solutions of the proposed system with initial conditions from domain Ω remain in this domain.

Theorem 2.1. *Let* $(S, E, I, R, S_k, E_k, I_k)$ *be any solution of system* (2.1) *with nonnegative initial conditions* (2.2). *For* $t \geq 0$ *there is:*

$$\Omega = \left\{(S, E, I, R, S_k, E_k, I_k) \in \mathbb{R}^7_+, V_1 \leq \frac{aN_0}{a' + b + c + d}, V_2 \leq \frac{a_k N_{0_k}}{a'_k + b_k + c_k}\right\}.$$

Then Ω *is a positively invariant and absorbing set for system* (2.1) *with initial conditions* (2.2).

Proof. To prove this theorem, we use the Lyapunov functions. Consider the following Lyapunov vector function $V(t) = (V_1(t), V_2(t))$. Suppose that functions $V_1(t)$, $V_2(t)$ are defined for $\forall\ t \geq 0$, and they are differentiable and continuously differentiable on set Ω containing the origin.

The time derivative of function $V(t)$ is equal to

$$\frac{dV(t)}{dt} = \begin{cases} \frac{dV_1(t)}{dt} &= aN_0 - (a' + b + c + d)V_1 - a'S - bE - cI - dR, \\ \frac{dV_2(t)}{dt} &= a_k N_{0_k} - (a'_k + b_k + c_k)V_2 - a'_k S_k - b_k E_k - c_k I_k. \end{cases} \tag{2.3}$$

For system (2.3), it is obvious that

$$\begin{aligned} \frac{dV_1(t)}{dt} &\leq aN_0 - (a' + b + c + d)V_1, \\ \frac{dV_2(t)}{dt} &\leq a_k N_{0_k} - (a'_k + b_k + c_k)V_2. \end{aligned} \tag{2.4}$$

By the properties of the Lyapunov function, we obtain the following conditions:

$$\begin{cases} \frac{dV_1}{dt} &\leq aN_0 - (a' + b + c + d)V_1 \leq 0, \\ \frac{dV_2}{dt} &\leq a_k N_{0_k} - (a'_k + b_k + c_k)V_2 \leq 0. \end{cases}$$

$\Rightarrow$

$$\begin{cases} V_1 &\geq \frac{aN_0}{a' + b + c + d}, \\ V_2 &\geq \frac{a_k N_{0_k}}{a'_k + b_k + c_k}. \end{cases} \tag{2.5}$$

From conditions (2.5), it follows that $\frac{dV(t)}{dt} \leq 0$, which means that Ω is a positively invariant and absorbing set.

From the above inequalities and conditions (2.3), we obtain the inequalities for V_1 and V_2:

$$\begin{aligned} 0 \leq V_1(t) &\leq \frac{aN_0}{a' + b + c + d} + e^{-(a' + b + c + d)t}\left(V_{0_1} - \frac{aN_0}{a' + b + c + d}\right), \\ 0 \leq V_2(t) &\leq \frac{a_k N_{0_k}}{a'_k + b_k + c_k} + e^{-(a'_k + b_k + c_k)t}\left(V_{0_2} - \frac{a_k N_{0_k}}{a'_k + b_k + c_k}\right). \end{aligned}$$

Using $t \longrightarrow +\infty$ we obtain

$$\begin{aligned} 0 \leq V_1(t) &\leq \frac{aN_0}{a' + b + c + d}, \\ 0 \leq V_2(t) &\leq \frac{a_k N_{0_k}}{a'_k + b_k + c_k}, \end{aligned}$$

and we can conclude that Ω is an absorbing set. Indeed, the following inequalities hold for $t \longrightarrow +\infty$:

$$\begin{aligned} \limsup_{t \to +\infty} V_1 &\leq \frac{aN_0}{a' + b + c + d}, \\ \limsup_{t \to +\infty} V_2 &\leq \frac{a_k N_{0_k}}{a'_k + b_k + c_k}. \end{aligned}$$

Thus, Ω is positively invariant, and all solutions are bounded by the interval $[0, \infty)$. □

2.1.3 Equilibrium points

For the presented model, we study two equilibrium points for a system of differential equations (2.1):

1. Equilibrium without diseases E_s;
2. Endemic equilibrium E_e, when the disease is present in the population, and the size of all subpopulations is nonzero.

Solving the following system of differential equations

$$\begin{cases} -\alpha S(t)I_k(t) + aN(t) - a'S(t) &= 0, \\ \alpha S(t)I_k(t) + \mu R(t) - bE(t) - \beta E(t) &= 0, \\ \beta E(t) - cI(t) - \gamma I(t) &= 0, \\ \gamma I(t) - dR(t) - \mu R(t) &= 0, \\ -\alpha_k S_k(t)I(t) + a_k N_k(t) - a'_k S_k(t) &= 0, \\ \alpha_k S_k(t)I(t) - b_k E_k(t) - \beta_k E_k(t) &= 0, \\ \beta_k E_k(t) - c_k I_k(t) &= 0, \end{cases} \tag{2.6}$$

find these two equilibrium points:

1. Equilibrium without diseases $E_s = (\frac{a}{a'}N_0, 0, 0, 0, \frac{a_k}{a'_k}N_{0_k}, 0, 0)$, i.e. this is a solution to the system withoutdisease, and only the number of susceptible human and mosquito subpopulations is nonzero.
2. Endemic equilibrium of system $E_e = (S^*, E^*, I^*, R^*, S_k^*, E_k^*, I_k^*)$, in which the disease is present in the population, and the number of all human and mosquito subpopulations is nonzero.

To find the second equilibrium, from the first equation of (2.6) we get $S = \dfrac{(aN_0)E}{\alpha I_k + a'}$, from the third equation we get $E = \dfrac{c+\gamma}{\beta}I$ or $I = \dfrac{\beta}{c+\gamma}E$, then from the fourth equation: $R = \dfrac{\gamma}{d+\mu}I$, from the fifth equation: $S_k = \dfrac{a_k N_{0_k}}{\alpha_k I + a'k}$, from the sixth equation: $E_k = \dfrac{\alpha_k S_k}{b_k + \beta_k}I$, from the seventh equation : $I_k = \dfrac{\beta_k E_k}{c_k}$, from the second equation: $E = \dfrac{\alpha}{b+\beta}SI_k + \dfrac{\mu}{b+\beta}R$.

Substituting the first, third, fourth, fifth, sixth and seventh equations of (2.6) into the second equation of this system, we obtain

$$E = \frac{aa_k\alpha\alpha_k\beta_k N_0 N_{0_k}(d+\mu)(c+\gamma)I}{((b+\beta)(d+\mu)(c+\gamma)-\mu\gamma\beta)(\alpha\beta_k\alpha_k a_k N_k I + a'c_k(b_k+\beta_k)(\alpha_k I + a'_k))}.$$

Given the third equation in the system (2.6), we get:

$$I = \frac{aa_k\alpha\beta\alpha_k\beta_k N_0 N_{0_k}(d+\mu) - a'a'_k c_k(b_k+\beta_k)((b+\beta)(d+\mu)(c+\gamma)-\mu\gamma\beta)}{((b+\beta)(d+\mu)(c+\gamma)-\mu\gamma\beta)(\alpha\beta_k\alpha_k a_k N_k + a'c_k\alpha_k(b_k+\beta_k))}.$$

Therefore, endemic equilibrium of (2.1) is defined by vector
$E_e = (S^*, E^*, I^*, R^*, S_k^*, E_k^*, I_k^*)$ with components

$$\begin{aligned}
I^* &= \frac{aa_k\alpha\beta\alpha_k\beta_k N_0 N_{0_k} - a'a'_k c_k(b_k+\beta_k)((b+\beta)(d+\mu)(c+\gamma)-\mu\gamma\beta)}{((b+\beta)(d+\mu)(c+\gamma)-\mu\gamma\beta)(\alpha\beta_k\alpha_k a_k N_k + a'c_k\alpha_k(b_k+\beta_k))},\\
S^* &= \frac{aN_0}{\alpha I_k^* + a'},\\
E^* &= \frac{c+\gamma}{\beta}I^*,\\
R^* &= \frac{\gamma}{d+\mu}I^*,\\
S_k^* &= \frac{a_k N_{0_k}}{\alpha_k I^* + a'_k},\\
E_k^* &= \frac{\alpha_k}{b_k+\beta_k}S_k^* I^*,\\
I_k^* &= \frac{a_k\alpha_k\beta_k N_{0_k}}{c_k(b_k+\beta_k)(\alpha_k I^* + a'_k)}I^*.
\end{aligned}$$

Equilibrium E_e represents an endemic equilibrium point of the model, in which all subgroups of the population are represented.

2.1.4 Determining basic reproduction number R_0

Basic reproductive number R_0 indicates an average number of new cases of malaria infection caused by one infected person in fully susceptible population. To calculate R_0 for a system of equations (2.1), we use a *method of next-generation matrix* described in $[29-32]$. For a system of equations (2.1) we can write:

$$\begin{aligned}
\frac{dx}{dt} &= F(x) - V(x),\\
x &= (S, E, I, R, S_k, E_k, I_k)^T.
\end{aligned}$$

Using the next generation method, we will perform the following calculations. First we define matrices F and V:

$$\mathcal{F} = \begin{pmatrix} \alpha_k S_k(t) I(t) \\ 0 \\ \alpha S(t) I_k(t) \\ 0 \end{pmatrix}, \quad \mathcal{V}^+ = \begin{pmatrix} \mu R(t) \\ \beta E(t) \\ 0 \\ \beta_k E_k(t) \end{pmatrix}, \quad \mathcal{V}^- = \begin{pmatrix} -(b+\beta)E(t) \\ -(c+\gamma)I(t) \\ -(b_k+\beta_k)E_k(t) \\ -c_k I_k(t) \end{pmatrix},$$

hence we get

$$\mathcal{V} = \mathcal{V}^+ + \mathcal{V}^- = \begin{pmatrix} \mu R(t) - (b+\beta)E(t) \\ \beta E(t) - (c+\gamma)I(t) \\ -(b_k+\beta_k)E_k(t) \\ \beta_k E_k(t) - c_k I_k(t) \end{pmatrix}.$$

Find matrices

$$D\mathcal{F}(E_s) = \begin{pmatrix} 0 & \alpha_k S_k^0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \alpha S^0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$D\mathcal{V}(E_s) = \begin{pmatrix} -(b+\beta) & 0 & 0 & 0 \\ \beta & -(c+\gamma) & 0 & 0 \\ 0 & 0 & -(b_k+\beta_k) & 0 \\ 0 & 0 & \beta_k & -c_k \end{pmatrix}.$$

Hence,

$$F = \begin{bmatrix} 0 & \alpha_k S_k^0 \\ 0 & 0 \end{bmatrix}, \quad F' = \begin{bmatrix} 0 & \alpha S^0 \\ 0 & 0 \end{bmatrix},$$
$$V = \begin{bmatrix} -(b+\beta) & 0 \\ \beta & -(c+\gamma) \end{bmatrix}, \quad V' = \begin{bmatrix} -(b_k+\beta_k) & 0 \\ \beta_k & -c_k \end{bmatrix}.$$

Calculate R_0 using formula $R_0 = \rho(-FV^{-1})$, where

$$V^{-1} = \frac{1}{det(V)} t_{(com(V))},$$

and

$$det(V) = (b+\beta)(c+\gamma), \quad t_{(com(V))} = \begin{bmatrix} -(c+\gamma) & 0 \\ -\beta & -(b+\beta) \end{bmatrix}.$$

Substituting $det(V)$ and $t_{(com(V))}$ into expression V^{-1}, we get

$$V^{-1} = \frac{1}{(b+\beta)(c+\gamma)} \begin{bmatrix} -(c+\gamma) & 0 \\ -\beta & -(b+\beta) \end{bmatrix},$$
$$(V')^{-1} = \frac{1}{(b_k+\beta_k)c_k} \begin{bmatrix} -c_k & 0 \\ -\beta_k & -(b_k+\beta_k) \end{bmatrix}.$$

Finally, we get the following expressions:

$$FV^{-1} = \begin{bmatrix} -\frac{\alpha_k \beta S_k^0}{(b+\beta)(c+\gamma)} & -\frac{\alpha_k S_k^0}{c+\gamma} \\ 0 & 0 \end{bmatrix},$$
$$FV'^{-1} = \begin{bmatrix} -\frac{\alpha\beta_k S^0)}{c_k(b_k+\beta_k)} & -\frac{\alpha S^0}{c_k} \\ 0 & 0 \end{bmatrix},$$

and calculate R_h and R_k:

$$R_h = \rho(-FV^{-1}) = \frac{\alpha_k \beta S_k^0}{(b+\beta)(c+\gamma)}, \quad R_k = \rho(-FV'^{-1}) = \frac{\alpha\beta_k S^0)}{c_k(b_k+\beta_k)},$$

hence we finally obtain basic reproductive number R_0 in the form:

$$R_0 = R_h \times R_k = \frac{\alpha_k \beta S_k^0 \alpha\beta_k S^0}{c_k(b_k+\beta_k)(b+\beta)(c+\gamma)},$$

where $(S^0, S_k^0) = (\frac{a}{a'}N_0, \frac{a_k}{a'_k}N_{0_k})$, and finally write the formula for R_0:

$$R_0 = \frac{\alpha\beta\alpha_k\beta_k a a_k N_0 N_{0_k}}{a' a'_k c_k (b+\beta)(c+\gamma)(b_k+\beta_k)}.$$

If $R_0 \leq 1$ and at least one person is infected, then the epidemic will not develop, and system (2.1) is stable. If $R_0 \geq 1$, i.e. at least one infected person can infect several people, the number of infected people is growing, and the disease can affect the entire population. A numerical study will give us a more representative picture of disease spread among population depending on a value of R_0.

Note that endemic equilibrium point E_e exists if $R_0 > 1$.

2.1.5 Examining stability of equilibrium points

First, let us analyze the stability of disease-free equilibrium of a system of equations (2.1), using basic reproductive number R_0, we formulate the result as a theorem.

Theorem 2.2. *Disease-free equilibrium E_s is locally asymptotically stable if $R_0 \leq 1$ and*

$$c_k > \frac{\alpha\beta\alpha_k\beta_k N_0 N_{0_k}(d+\mu)}{(b+\beta)(c+\gamma)(d+\mu)(b_k+\beta_k)+\beta\gamma\mu(b_k+\beta_k)},$$

and unstable if $R_0 > 1$.

Proof. The Jacobi matrix of system (2.1) is written as:
$J(S, E, I, R, S_k, E_k, I_k) =$

$$\begin{pmatrix} -\alpha I_k - a' & 0 & 0 & 0 & 0 & 0 & -\alpha S \\ \alpha I_k & -b-\beta & 0 & \mu & 0 & 0 & \alpha S \\ 0 & \beta & -c-\gamma & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & -d-\mu & 0 & 0 & 0 \\ 0 & 0 & -\alpha_k S_k & 0 & \alpha_k I - a'_k & 0 & 0 \\ 0 & 0 & \alpha_k S_k & 0 & \alpha_k I & -(b_k+\beta_k) & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_k & -c_k \end{pmatrix}.$$

The Jacobi matrix at disease-free equilibrium point E_s is equal to

$$J(E_s) = \begin{pmatrix} -a' & 0 & 0 & 0 & 0 & 0 & -\alpha\frac{N_0}{a} \\ 0 & -b-\beta & 0 & \mu & 0 & 0 & \alpha\frac{N_0}{a} \\ 0 & \beta & -c-\gamma & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & -d-\mu & 0 & 0 & 0 \\ 0 & 0 & -\alpha_k\frac{N_{0_k}}{a_k} & 0 & -a'_k & 0 & 0 \\ 0 & 0 & \alpha_k\frac{N_{0_k}}{a_k} & 0 & 0 & -(b_k+\beta_k) & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_k & -c_k \end{pmatrix}.$$

We determine the eigenvalues of this matrix by equating its determinant to zero,

$$\begin{vmatrix} -a'-\lambda & 0 & 0 & 0 & 0 & 0 & -\alpha\frac{N_0}{a} \\ 0 & -b-\beta-\lambda & 0 & \mu & 0 & 0 & \alpha\frac{N_0}{a} \\ 0 & \beta & -c-\gamma-\lambda & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & -d-\mu-\lambda & 0 & 0 & 0 \\ 0 & 0 & -\alpha_k\frac{N_{0_k}}{a_k} & 0 & -a'_k-\lambda & 0 & 0 \\ 0 & 0 & \alpha_k\frac{N_{0_k}}{a_k} & 0 & 0 & -(b_k+\beta_k)-\lambda & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_k & -c_k-\lambda \end{vmatrix}$$

We get the characteristic equation

$$(a'+\lambda)(a'_k+\lambda)[\lambda^5 + C_1\lambda^4 + C_2\lambda^3 + C_3\lambda^2 + C_4\lambda + C_5] = 0,$$

where

$$
\begin{aligned}
C_1 &= c_k + d + \mu + b_k + \beta_k + b + \beta + c + \gamma,\\
C_2 &= (d+\mu)(b_k+\beta_k) + (b+\beta+c+\gamma)(d+\mu+b_k+\beta_k)\\
&\quad + (b+\beta)(c+\gamma) + c_k(d+\mu+b_k+\beta_k),\\
C_3 &= (b+\beta+c+\gamma)((d+\mu)(b_k+\beta_k) + c_k(d+\mu+b_k+\beta_k))+\\
&\quad + (b+\beta)(c+\gamma)(d+\mu+b_k+\beta_k+c_k) + c_k(d+\mu)(b_k+\beta_k),\\
C_4 &= (b+\beta)(c+\gamma)((d+\mu)(b_k+\beta_k) + c_k(d+\mu+b_k+\beta_k)\\
&\quad + \beta\gamma\mu(c_k+b_k+\beta_k) - \frac{\alpha\beta\alpha_k\beta_k N_0 N_{0_k}}{aa_k},\\
C_5 &= c_k(b+\beta)(c+\gamma)(d+\mu)(b_k+\beta_k) + \beta\gamma\mu c_k(b_k+\beta_k) - \alpha\beta\alpha_k\beta_k N_0 N_{0_k}(d+\mu).
\end{aligned}
$$

The characteristic equation has seven eigenvalues, the first two of which λ_1 and λ_2 are: $\lambda_1 = -a'$ and $\lambda_2 = -a'_k$. The remaining five eigenvalues are obtained by solving the equation:

$$\lambda^5 + C_1\lambda^4 + C_2\lambda^3 + C_3\lambda^2 + C_4\lambda + C_5 = 0.$$

The solution to this equation is difficult to write in an explicit form. To determine the nature of the stability of equilibrium point E_s. We use the Routh-Hurwitz criterion to study stability. To do this, we write an auxiliary matrix:

$$
\begin{vmatrix}
1 & C_2 & C_4 & 0 & 0 & 0\\
C_1 & C_3 & C_5 & 0 & 0 & 0\\
\dfrac{C_1C_2 - C_3}{C_1} & \dfrac{C_1C_4 - C_5}{C_1} & 0 & 0 & 0 & 0\\
C_3 - \dfrac{C_1C_4 - C_5}{C_1C_2 - C_3} & C_5 & 0 & 0 & 0 & 0\\
\dfrac{C_1C_4 - C_5}{C_1} - \dfrac{C_5(C_1C_2 - C_3)^2}{C_3(C_1C_2 - C_3) - C_1C_4 + C_5} & 0 & 0 & 0 & 0 & 0\\
C_5 & 0 & 0 & 0 & 0 & 0
\end{vmatrix}.
$$

Applying the Routh-Hurwitz criterion, we obtain that system (2.1) is asymptotically

stable at equilibrium point E_s if the inequalities

$$\begin{aligned} C_1 &> 0, \\ C_5 &> 0, \\ \frac{C_1C_2 - C_3}{C_1} &> 0, \\ C_3 - \frac{C_1C_4 - C_5}{C_1C_2 - C_3} &> 0, \\ \frac{C_1C_4 - C_5}{C_1} - \frac{C_5(C_1C_2 - C_3)^2}{C_3(C_1C_2 - C_3) - C_1C_4 + C_5} &> 0 \end{aligned}$$

are satisfied.

Then from $\frac{C_1C_2-C_3}{C_1} > 0$ and $C_1 > 0$ it follows that $C_1C_2 - C_3 > 0$. The fourth inequality is equivalent to $C_3(C_1C_2 - C_3) - C_1C_4 + C_5 > 0$ or $C_1C_2C_3 - C_1C_4 - C_3^2 + C_5 > 0$. Then the last inequality can be written as: $(C_1C_4 - C_5)(C_1C_2C_3 - C_1C_4 - C_3^2 + C_5) - C_1C_5(C_1C_2 - C_3)^2 > 0$.

Therefore, we get the system:

$$\begin{aligned} C_1 &> 0, \\ C_5 &> 0, \\ C_1C_2 - C_3 &> 0, \\ C_1C_2C_3 - C_1C_4 - C_3^2 + C_5 &> 0, \\ (C_1C_4 - C_5)(C_1C_2C_3 - C_1C_4 - C_3^2 + C_5) - C_1C_5(C_1C_2 - C_3)^2 &> 0. \end{aligned}$$

The first two eigenvalues λ_1 and λ_2 have negative real parts. The remaining five eigenvalues have negative real parts if they satisfy the Routh-Hurwitz criterion. Thus, all eigenvalues of the characteristic equation have negative real parts if and only if $R_0 < 1$ and $C_1C_2C_3 + C_5 > C_1C_4 + C_3^2$, i.e.

$$c_k > \frac{\alpha\ beta\alpha_k\beta_k N_0 N_{0_k}(d+\mu)}{(b+\beta)(c+\gamma)(d+\mu)(b_k+\beta_k) + \beta\gamma\mu(b_k+\beta_k)},$$

then disease-free equilibrium E_s is locally asymptotically stable. The theorem is proved. □

Theorem 2.3. *Endemic equilibrium E_e is locally asymptotically stable if $R_0 > 1$ and $c_k > \frac{\alpha\beta\beta_k\alpha_k S_k^*}{(\alpha_k I^* + a'k)(a' + \alpha I_k^*)(b_k+\beta_k)}$.*

Proof. The Jacobi matrix of system (2.1) is written as:
$J(S, E, I, R, S_k, E_k, I_k) =$

$$\begin{pmatrix} -\alpha I_k - a' & 0 & 0 & 0 & 0 & 0 & -\alpha S \\ \alpha I_k & -b-\beta & 0 & \mu & 0 & 0 & \alpha S \\ 0 & \beta & -c-\gamma & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & -d-\mu & 0 & 0 & 0 \\ 0 & 0 & -\alpha_k S_k & 0 & \alpha_k I - a'_k & 0 & 0 \\ 0 & 0 & \alpha_k S_k & 0 & \alpha_k I & -(b_k+\beta_k) & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_k & -c_k \end{pmatrix}.$$

The Jacobi matrix at endemic equilibrium $E_e = (S^*, E^*, I^*, R^*, S_k^*, E_k^*, I_k^*)$ is

$$J(E_e) = \begin{pmatrix} -\alpha I_k^* - a' & 0 & 0 & 0 & 0 & 0 & -\alpha S^* \\ \alpha I_k^* & -b-\beta & 0 & \mu & 0 & 0 & \alpha S^* \\ 0 & \beta & -c-\gamma & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & -d-\mu & 0 & 0 & 0 \\ 0 & 0 & -\alpha_k S_k^* & 0 & \alpha_k I^* - a'_k & 0 & 0 \\ 0 & 0 & \alpha_k S_k^* & 0 & \alpha_k I^* & -(b_k+\beta_k) & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_k & -c_k \end{pmatrix}.$$

Let us find the eigenvalues of this matrix by equating its determinant to zero, and we obtain the following characteristic equation:

$$\lambda^7 + A_1\lambda^6 + A_2\lambda^5 + A_3\lambda^4 + A_4\lambda^3 + A_5\lambda^2 + A_6\lambda + A_7 = 0,$$

where

$$
\begin{aligned}
A_1 &= b+\beta+c+\gamma+d+\mu+a'+\alpha I_k^*+b_k+\beta_k+\alpha_k I^*+a_k'+c_k,\\
A_2 &= (d+\mu)(b+\beta+c+\gamma)+(b+\beta)(c+\gamma)+(b+\beta+c+\gamma+d+\mu+a'\\
&\quad+\alpha I_k^*+b_k+\beta_k+\alpha_k I^*+a_k'+c_k)+c_k(\alpha_k I^*+a_k')+(\alpha I_k^*+a')(b_k+\beta_k)\\
&\quad+(a'+\alpha I_k^*+b_k+\beta_k)(\alpha_k I^*+a_k'+c_k),\\
A_3 &= (d+\mu)(b+\beta)(c+\gamma)+(d+\mu)(b+\beta+c+\gamma)+(b+\beta)(c+\gamma)+a'\\
&\quad+\alpha I_k^*+b_k+\beta_k+\alpha_k I^*+a_k'+c_k+c_k(\alpha_k I^*+a_k')+(\alpha I_k^*+a')(b_k+\beta_k)\\
&\quad+(a'+\alpha I_k^*+b_k+\beta_k)(\alpha_k I^*+a_k'+c_k)(b+\beta+c+\gamma+d+\mu)\\
&\quad+c_k(\alpha_k I^*+a_k')(a'+\alpha I_k^*+b_k+\beta_k)+(\alpha I_k^*+a')(b_k+\beta_k)(\alpha_k I^*+a_k'+c_k),\\
A_4 &= (a'+\alpha I_k^*+b_k+\beta_k+\alpha_k I^*+a_k'+c_k)(d+\mu)(b+\beta)(c+\gamma)\\
&\quad+[c_k(\alpha_k I^*+a_k')+(\alpha I_k^*+a')(b_k+\beta_k)+(a'+\alpha I_k^*+b_k+\beta_k)(\alpha_k I^*+a_k'+c_k)]\\
&\quad\times[(d+\mu)(b+\beta+c+\gamma)+(b+\beta)(c+\gamma)]+(b+\beta+c+\gamma+d+\mu)\\
&\quad\times[c_k(\alpha_k I^*+a_k')(a'+\alpha I_k^*+b_k+\beta_k)+(\alpha I_k^*+a')(b_k+\beta_k)(\alpha_k I^*+a_k'+c_k)]\\
&\quad+c_k(\alpha_k I^*+a_k')(a'+\alpha I_k^*)(b_k+\beta_k)-\alpha\beta\beta_k\alpha_k S_k^*,\\
A_5 &= [c_k(\alpha_k I^*+a_k')(a'+\alpha I_k^*)(b_k+\beta_k)+(a'+\alpha I_k^*+b_k+\beta_k)(\alpha_k I^*+a_k'+c_k)]\\
&\quad\times(b+\beta)(c+\gamma)(d+\mu)+[c_k(\alpha_k I^*+a_k')(a'+\alpha I_k^*+b_k+\beta_k)+c_k(\alpha_k I^*+a_k')\\
&\quad\times(a'+\alpha I_k^*)(b_k+\beta_k)(\alpha_k I^*+a_k'+c_k)][(d+\mu)(b+\beta+c+\gamma)+(b+\beta)(c+\gamma)]\\
&\quad+c_k(b+\beta+c+\gamma+d+\mu)(\alpha_k I^*+a_k')(a'+\alpha I_k^*)(b_k+\beta_k)\\
&\quad-\alpha\beta\beta_k\alpha_k S_k^*(d+\mu+a_k'+\alpha S^* I^*+\alpha I_k^*+a'),\\
A_6 &= (d+\mu)(b+\beta)(c+\gamma)[c_k(\alpha_k I^*+a_k')(a'+\alpha I_k^*+b_k+\beta_k)\\
&\quad+(\alpha I_k^*+a')(b_k+\beta_k)(\alpha_k I^*+a_k'+c_k)]+c_k(\alpha_k I^*+a_k')(a'+\alpha I_k^*)(b_k+\beta_k)\\
&\quad\times[(d+\mu)(b+\beta+c+\gamma)+(b+\beta)(c+\gamma)]\\
&\quad-\alpha\beta\beta_k\alpha_k S_k^*(a_k'(d+\mu)+(d+\mu+a_k')(\alpha S^* I^*+\alpha I_k^*+a')),\\
A_7 &= c_k(\alpha_k I^*+a_k')(a'+\alpha I_k^*)(b_k+\beta_k)(d+\mu)(b+\beta)(c+\gamma)\\
&\quad-\alpha\beta\beta_k\alpha_k S_k^* a_k'(d+\mu)(\alpha S^* I^*+\alpha I_k^*+a').
\end{aligned}
$$

The eigenvalues of this matrix are solutions of the characteristic equation. The equation has seven roots. We use the Routh-Hurwitz criterion, which states that all roots of the characteristic equation have negative real parts if and only if the conditions of the Routh-Hurwitz criterion are satisfied.

We write an auxiliary matrix:

$$\begin{vmatrix} 1 & A_2 & A_4 & A_6 & 0 & 0 \\ A_1 & A_3 & A_5 & A_7 & 0 & 0 \\ \dfrac{A_1A_2-A_3}{A_1} & \dfrac{A_1A_4-A_5}{A_1} & \dfrac{A_1A_6-A_7}{A_1} & 0 & 0 & 0 \\ A_3-\dfrac{A_1(A_1A_4-A_5)}{A_1A_2-A_3} & A_5-\dfrac{A_1(A_1A_6-A_7)}{A_1A_2-A_3} & A_7 & 0 & 0 & 0 \\ A_1' & A_2' & 0 & 0 & 0 & 0 \\ A_3' & A_7 & 0 & 0 & 0 & 0 \\ \frac{A_3'A_2'-A_1'A_7}{A_3'} & 0 & 0 & 0 & 0 & 0 \\ A_7 & 0 & 0 & 0 & 0 & 0, \end{vmatrix},$$

where

$$A_1' = \frac{A_1A_4-A_5}{A_1} - \frac{(A_1A_2-A_3)(A_5(A_1A_2-A_3)-A_1(A-1A_6-A_7))}{A_1(A_3(A_1A_2-A_3)-A_1(A_1A_4-A_5))},$$
$$A_2' = \frac{A_1A_6-A_7}{A_1} - \frac{A_7(A_1A_2-A_3)^2}{A_1(A_3(A_1A_2-A_3)-A_1(A_1A_4-A_5))},$$
$$A_3' = A_5 - \frac{A_1(A_1A_6-A_7)}{A_1A_2-A_3} - \frac{A_3(A_1A_2-A_3)-A_1(A_1A_4-A_5)}{A_1A_2-A_3}\frac{A_2'}{A_1'}.$$

Applying the Routh-Hurwitz criterion, we obtain that system (2.1) is asymptotically stable at equilibrium point E_e if the following inequalities hold:

$$A_1 > 0,$$
$$A_7 > 0,$$
$$\frac{A_1A_2-A_3}{A_1} > 0,$$
$$A_3 - \frac{A_1(A_1A_4-A_5)}{A_1A_2-A_3} > 0,$$
$$\frac{A_1A_4-A_5}{A_1} - \frac{(A_1A_2-A_3)(A_5(A_1A_2-A_3)-A_1(A-1A_6-A_7))}{A_1(A_3(A_1A_2-A_3)-A_1(A_1A_4-A_5))} > 0,$$
$$\frac{A_1A_6-A_7}{A_1} - \frac{A_7(A_1A_2-A_3)^2}{A_1(A_3(A_1A_2-A_3)-A_1(A_1A_4-A_5))} > 0,$$
$$A_5 - \frac{A_1(A_1A_6-A_7)}{A_1A_2-A_3} - \frac{A_3(A_1A_2-A_3)-A_1(A_1A_4-A_5)}{A_1A_2-A_3}\frac{A_2'}{A_1'} > 0$$
$$\frac{A_3'A_2'-A_1'A_7}{A_3'} > 0.$$

Then from $\frac{A_1A_2-A_3}{A_1} > 0$ and $A_1 > 0$ it follows that $A_1A_2 - A_3 > 0$. The fourth inequality is equivalent to $A_3(A_1A_2 - A_3) - A_1(A_1A_4 - A_5) > 0$, or $A_1A_2 - A_3 > 0$.

The fifth inequality is equivalent to $A_1(A_1A_4 - A_5)(A_3(A_1A_2 - A_3) - A_1(A_1A_4 - A_5)) - A_1(A_1A_2 - A_3)(A_5(A_1A_2 - A_3) - A_1(A_1A_2 - A_3) - 1A_6 - A_7)) > 0$ or $A_1^2(A_3(A_1A_2 - A_3) - A_1(A_1A_4 - A_5) > 0$. The sixth inequality is equivalent to $A_1(A_1A_6 - A_7)(A_3(A_1A_2 - A_3) - A_1(A_1A_4 - A_5)) - A_1A_7(A_1A_2 - A_3)^2 > 0$, or $A_1' > 0$. The seventh inequality is equivalent to $A_5A_1'(A_1A_2 - A_3) - A_1A_1'(A_1A_6 - A_7) - A_2'(A_3(A_1A_2 - A_3) - A_1(A_1A_4 - A_5)) > 0$. Then the last inequality can be simplified as $A_3'A_2' - A_1'A_7 > 0$, or $A_3' > 0$.

Therefore, we get the system:

$$\begin{aligned}
A_1 &> 0,\\
A_7 &> 0,\\
A_1A_2 - A_3 &> 0,\\
A_3(A_1A_2 - A_3) - A_1(A_1A_4 - A_5) &> 0,\\
A_1(A_1A_4 - A_5)(A_3(A_1A_2 - A_3) - A_1(A_1A_4 - A_5))-&\\
-A_1(A_1A_2 - A_3)(A_5(A_1A_2 - A_3) - A_1(A - 1A_6 - A_7)) &> 0,\\
A_1(A_1A_6 - A_7)(A_3(A_1A_2 - A_3) - A_1(A_1A_4 - A_5)) - A_1A_7(A_1A_2 - A_3)^2 &> 0,\\
A_5A_1'(A_1A_2 - A_3) - A_1A_1'(A_1A_6 - A_7) - A_2'(A_3(A_1A_2 - A_3)-&\\
-A_1(A_1A_4 - A_5)) &> 0\\
A_3'A_2' - A_1'A_7 &> 0,
\end{aligned}$$

Seven eigenvalues have negative real parts if they satisfy the Routh-Hurwitz criteria. Thus, all eigenvalues of the characteristic equation have negative real parts if and only if $R_0 > 1$ and $A_3A_1A_2 + A_1A_5 > A_3^2 + A_1^2A_4$,what is done when $c_k > \frac{\alpha\beta\beta_k\alpha_kS_k^*}{(\alpha_kI^*+a'k)(a'+\alpha I_k^*)(b_k+\beta_k)}$, then endemic equilibrium E_e is locally asymptotically stable. □

2.1.6 Numerical simulation

Let's simulate the malaria dynamics in the time interval $[0, 60]$ with different values of parameters, as a result, with different values of R_0. The curves are plotted using the Matlab software. The parameters for which numerical simulation is performed are presented in tables.

Fig. 2.2 presents the results of numerical simulation for two data sets, for which $R_0 = 2.44$ (the first line of graphs) and $R_0 = 10.45$ (the second line of graphs). The left graphs depict the dynamic process of human population development, the right

Table 2.1: Parameters for the simulation, which results are presented in Fig. 2.2.

α	α_k	β	β_k	γ	γ_k	μ	μ_k	a	a'	a_k	a'_k	b	b_k	c	c_k	d	d_k	R_0
Fig. 2.2 (first set of parameters)																		
0.9	0.7	1.2	0.5	0.4	0.5	0.15	0.2	0.3	0.2	0.4	0.3	0.3	0.7	0.03	0.4	0.15	0.25	2.44
Fig. 2.2 (second set of parameters)																		
1.8	0.5	1.5	0.6	0.3	0.5	0.1	0.15	0.6	0.3	0.4	0.2	0.5	0.65	0.01	0.4	0.12	0.17	10.45

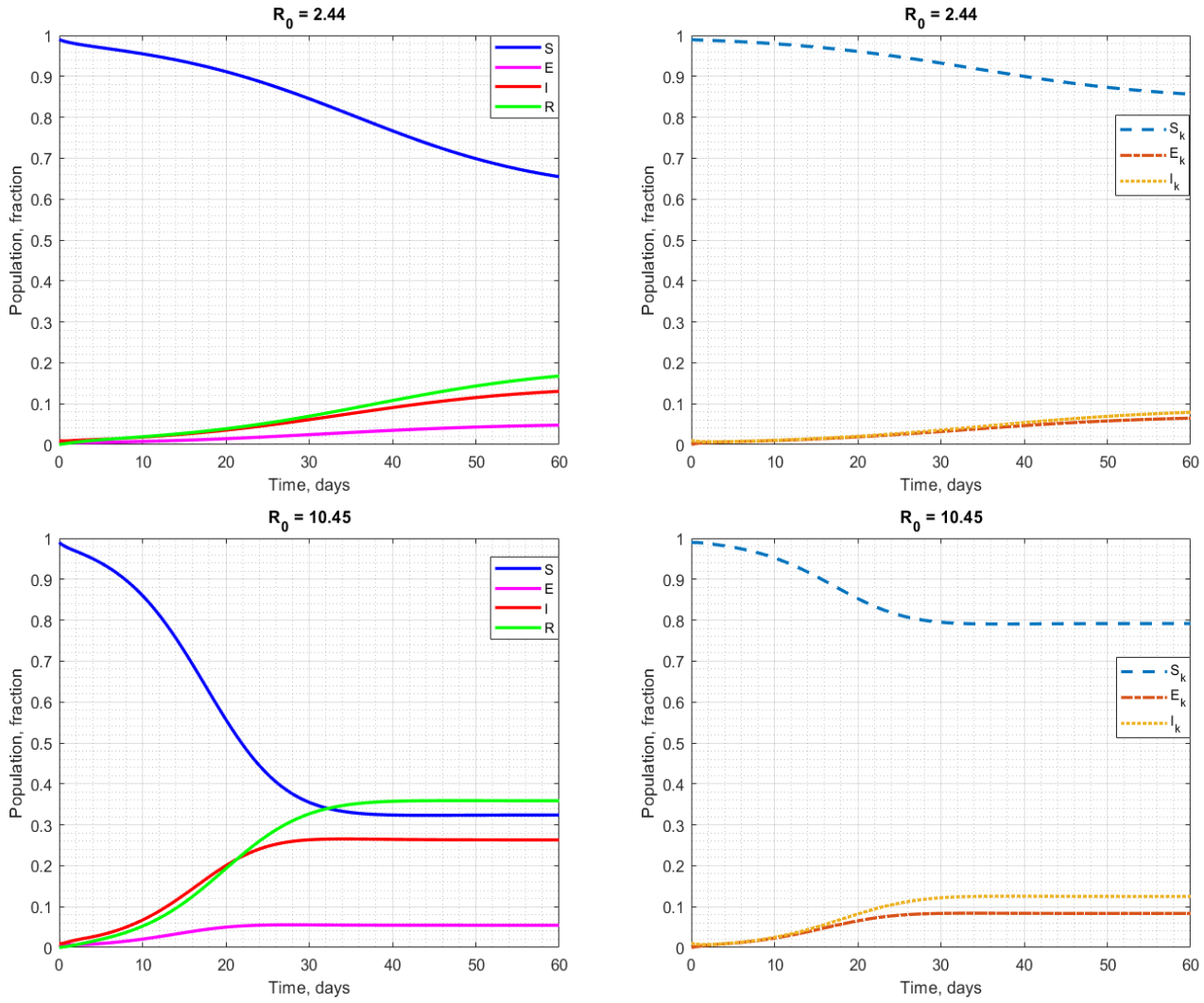

Figure 2.2: Epidemic process for different values $R_0 > 1$ ($R_0 = 2,44$ и $R_0 = 10,44$).

graphs show the dynamic process of mosquito population development. It can be seen that the disease exists in populations (hosts and vectors) and the susceptible subpopulation curves decrease. At the same time, the curves of subpopulations (exposed, infected and recovered) are gradually stabilizing, and a significant disease spread in population can be noted. If the epidemic process course is not influenced, there is a risk that the disease will remain in population, since the basic reproduction number shows that at least one infected person can infect several people (this is true for both cases).

Table 2.2: Parameters for the simulation, which results are presented in Fig. 2.3.

α	α_k	β	β_k	γ	γ_k	μ	μ_k	a	a'	a_k	a'_k	b	b_k	c	c_k	d	d_k	R_0
Fig. 2.3 (first set of parameters)																		
0.7	0.8	0.9	0.7	0.5	0.4	0.3	0.4	0.4	0.316	0.6	0.3	0.5	0.8	0.65	0.8	0.2	0.3	0.46
Fig. 2.3 (second set of parameters)																		
0.8	0.7	0.9	0.6	0.5	0.65	0.2	0.3	0.4	0.35	0.5	0.45	0.4	0.75	0.02	0.5	0.05	0.3	0.84

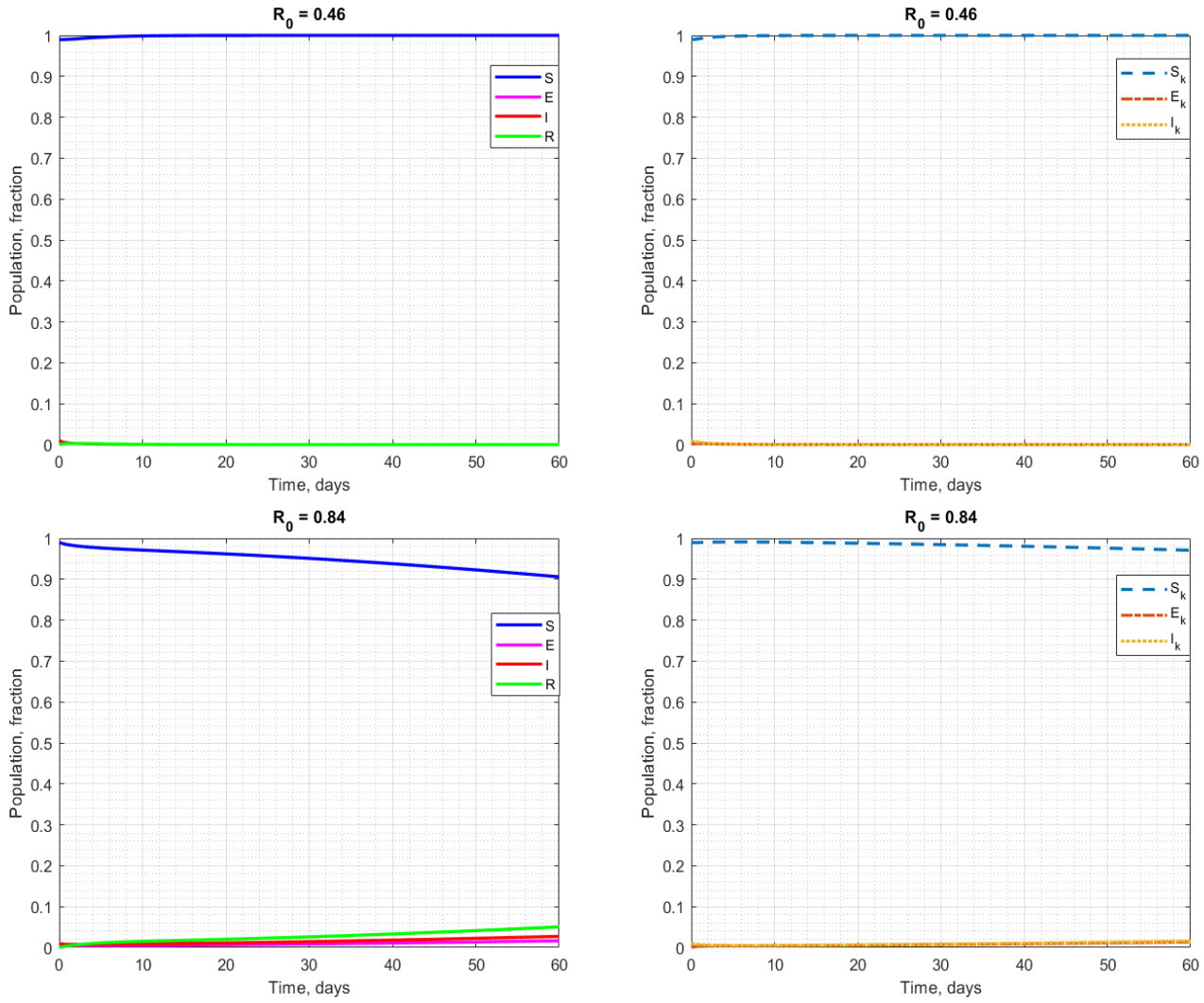

Figure 2.3: Epidemic process for different values $R_0 < 1$ ($R_0 = 0.46$ and $R_0 = 0.84$).

Fig. 2.3 presents the results of numerical simulation for two data sets, for which $R_0 = 0.46$ (first line of graphs) and $R_0 = 0.84$ (second line of graphs). The left graphs of Fig. 2.2 and Fig. 2.3 show the dynamic process of human population development. The right graphs of these figures show the dynamic process of mosquito population. We can observe that the disease is practically absent and all curves of subpopulations (hosts and vectors) are close to linear, i.e. subpopulation sizes are almost constant. The disease is not dangerous for the population for these parameter sets, since each infected person infects less than one person, which explains why

the disease can disappear from the population after some time.

Table 2.3: Parameters for the simulation, which results are presented in Fig. 2.4.

α	α_k	β	β_k	γ	γ_k	μ	μ_k	a	a'	a_k	a'_k	b	b_k	c	c_k	d	d_k	R_0
Fig. 2.4 (first set of parameters)																		
0.7	0.8	0.9	0.7	0.5	0.6	0.3	0.4	0.4	0.4	0.6	0.3	0.45	0.55	0.05	0.45	0.2	0.3	23.23
Fig. 2.4 (second set of parameters)																		
0.7	0.8	0.9	0.7	0.5	0.4	0.3	0.4	0.4	0.4	0.6	0.3	1.5	1.8	1.65	1.8	0.2	0.3	0.04

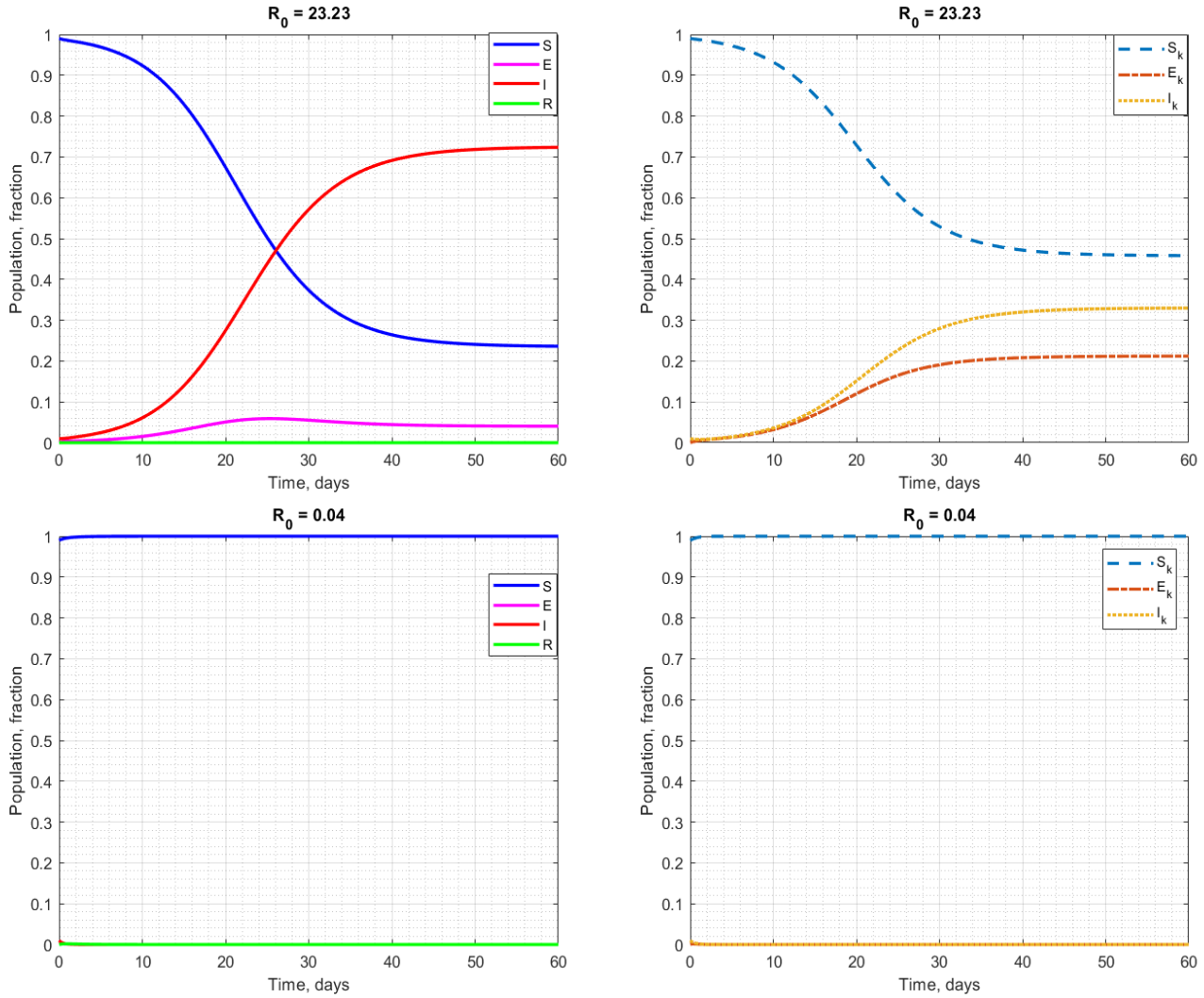

Figure 2.4: Epidemic process for different values R_0 ($R_0 = 23.23$ and $R_0 = 0.04$).

In Fig. 2.4 we present two simulation cycles for which $R_0 = 23.23$ (first line of graphs) and $R_0 = 0.04$ (second line of graphs). In the first stage of the simulation, we should notice that the size of infected subpopulations (both host and vector) increases significantly, as shown by the corresponding curve (the first line of graphs), which grows exponentially. The entire population is at risk of infection if measures are not taken to control the disease. In the second stage, we present the case when

$R_0 = 0.04$, i.e. the basic reproduction number is almost zero, which explains the absence of the disease. The population remains stable.

We can see that the basic reproductive number R_0 plays an important role in the epidemic process development. Numerical simulations show that measures are required to reduce the basic reproductive number in order to prevent the epidemic from developing rapidly in human and mosquito populations.

Malaria is a tropical infection disease. So far, scientists have not been able to develop an effective vaccine to fight this disease, which can be very dangerous and lead to many deaths in the population. Mathematical modeling of this disease plays an important role in understanding transmission dynamics and appreciate prevention strategies. The next section will present a model with vaccination of the population, which aims to reduce the number of new infected people, i.e. to decrease the basic reproductive number.

2.2 Vector-borne malaria epidemic model with vaccination

This section proposes a model for the development of the malaria epidemic process with direct transmission in vaccination.

2.2.1 Mathematical model

Let there be two populations: a host (human population) and a vector (mosquito population) that have been vaccinated to reduce disease. Vaccination is expressed as a percentage. Note that dv is the percentage of vaccination performed in host population, and σ is a reduction rate of malaria infected mosquitoes by a set of methods used to eliminate or prevent mosquito development.

The model shown in Fig. 2.5 is based on the following hypotheses:

1. Absence of migration of individuals in the population;
2. Assumption that the sizes of both populations (human and mosquito) are not constant during a study interval;
3. Relatively short lifespan (an infected mosquito does not have time to recover);
4. Assumption that a susceptible person becomes contagious after an infected mosquito bite and becomes susceptible again after recovery; and a healthy mosquito becomes infected after it bites an infected person.

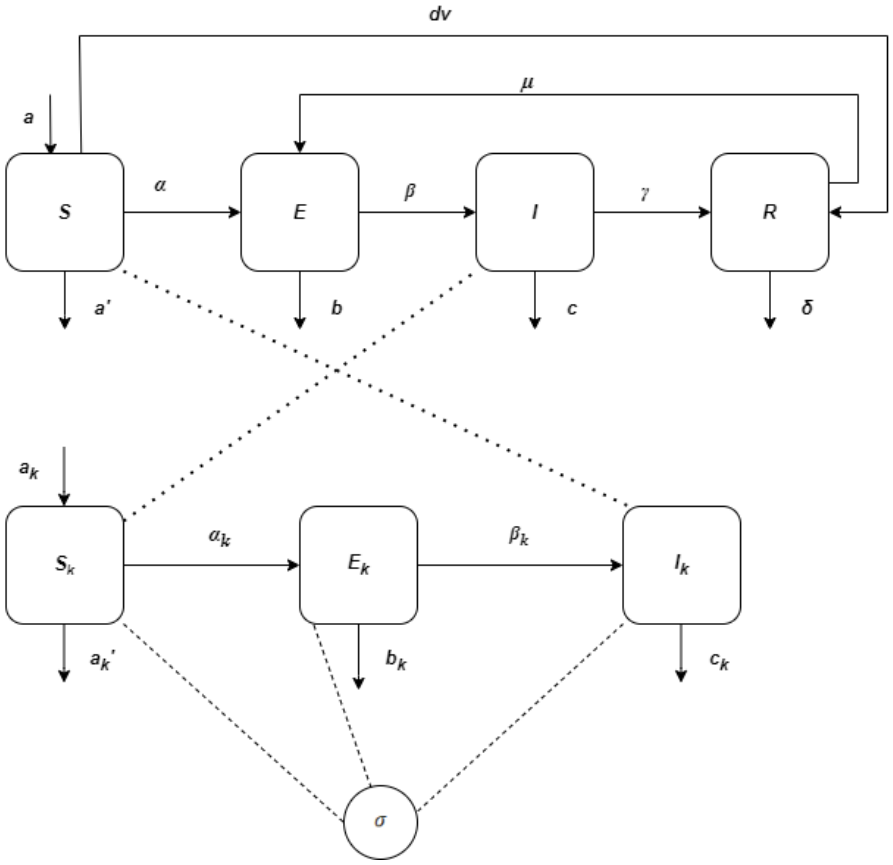

Figure 2.5: Vector-borne model with vaccination

The total host population can be represented as $N(t) = S(t) + E(t) + I(t) + R(t)$ and the total vector population can be represented as $N_k(t) = S_k(t) + E_k(t) + I_k(t)$.

The mathematical model of population dynamics (human and mosquito) can be represented analytically by the following nonlinear system of seven ordinary differential equations:

$$\begin{cases} \frac{dS(t)}{dt} &= -\alpha S(t)I_k(t) + aN_0(t) - a'S(t) - dvS(t), \\ \frac{dE(t)}{dt} &= \alpha S(t)I_k(t) + \mu R(t) - bE(t) - \beta E(t), \\ \frac{dI(t)}{dt} &= \beta E(t) - cI(t) - \gamma I(t), \\ \frac{dR(t)}{dt} &= \gamma I(t) - \delta R(t) - \mu R(t) + dvS(t), \\ \frac{dS_k(t)}{dt} &= -\alpha_k S_k(t)I(t) + a_k N_{k_0}(t) - a'_k S_k(t) - \sigma S_k(t), \\ \frac{dE_k(t)}{dt} &= \alpha_k S_k(t)I(t) - b_k E_k(t) - \beta_k E_k(t) - \sigma E_k(t), \\ \frac{dI_k(t)}{dt} &= \beta_k E_k(t) - c_k I_k(t) - \sigma I_k(t), \end{cases} \tag{2.7}$$

with initial conditions

$$S(0) \geq 0,\ E(0) \geq 0,\ I(0) \geq 0,\ R(0) \geq 0,\ S_k(0) \geq 0,\ E_k(0) \geq 0,\ I_k(0) \geq 0. \tag{2.8}$$

The general dynamics of human population is represented by the equation:

$$\frac{dN}{dt} = aN_0 - a'S - bE - cI - \delta R.$$

Given initial conditions (2.8) must satisfy inequality: $N(0) \geq 0$. Thus, total population size $N(t)$ remains positive and limited during the entire time $t > 0$. The dynamics of mosquito population is as follows

$$\frac{dN_k}{dt} = aN_{0_k} - a'S_k - bE_k - cI_k - \sigma(S_k + E_k + I_k).$$

The model uses the following parameters:

- $N(t)$ — size of human population;
- $S(t)$ — size of subpopulation of susceptible individuals;
- $E(t)$ — size of subpopulation of exposed people;
- $I(t)$ — size of subpopulation of infected people;
- $R(t)$ — size of subpopulation of recovered people;
- a — birth rate in human population;
- a' — mortality rate among subpopulation S;
- b — mortality rate among subpopulation E;
- c — mortality rate among infected subpopulation I;
- δ — mortality rate among recovered subpopulation R;
- β — intensity of people's transition from subpopulation E to I with the onset of isease symptoms;
- γ — intensity of people's recovery, i.e. transition from subpopulation I to R;
- μ — rate of people's return from recovered to susceptible;
- α — probability of transmitting an infectious mosquito bite to a susceptible person.

- $N_k(t)$ — total mosquito population;
- $S_k(t)$ — number of mosquitoes that can be infected;
- $E_k(t)$ — number of mosquitoes susceptible to the disease;
- $I_k(t)$ — number of infected mosquitoes;
- $a_k(t)$ — birth rate in mosquito population;
- $a'_k(t)$ — mortality in susceptible mosquito population;
- $b_k(t)$ — mortality of exposed mosquito population;
- $c_k(t)$ — mortality of infected mosquito population;
- $\alpha_k(t)$ — probability of mosquito moving from susceptible to exposed group;
- $\beta_k(t)$ — coefficient of mosquitoes that begin to show disease symptoms;
- $dv \in (0, 1)$ — level of vaccination of susceptible part of population;
- σ — decrease level of mosquito population as a result of anti-epidemiological measures.

Region of admissible values

A mathematical model represented by a system of differential equations (2.7) describes changes in human and mosquito populations. Therefore, it is important to make sure that all solutions with nonnegative initial conditions (2.8) will remain nonnegative for any t. All solutions of the proposed system that have initial data in region Ω.

Theorem 2.4. *Let* $(S, E, I, R, S_k, E_k, I_k)$ *be any solution of system* (2.7) *with positive initial conditions* (2.8). *For any time* $t \geq 0$ *there exists:*

$$\Omega = \left\{(S, E, I, R, S_k, E_k, I_k) \in \mathbb{R}^7_+, V_1 \leq \frac{aN_0}{a' + b + c + \delta}, V_2 \leq \frac{a_k N_{0_k}}{a'_k + b_k + c_k + \sigma}\right\}.$$

Then Ω *is positively invariant and absorbing for system* (2.7) *with initial conditions* (2.8).

Proof. To prove the theorem, we use the Lyapunov functions. Consider the Lyapunov function $V(t) = (V_1(t), V_2(t))$. Suppose that functions $V_1(t)$, $V_2(t)$ are defined for $\forall\ t \geq 0$, they are also differentiable and continuously differentiable on set Ω containing the origin.

The time derivative of function $V(t)$ is equal to

$$\frac{dV(t)}{dt} = \begin{cases} \dfrac{dV_1(t)}{dt} &= aN_0 - (a' + b + c + \delta)V_1 - a'S - bE - cI - \delta R, \\ \dfrac{dV_2(t)}{dt} &= a_k N_{0_k} - (a'_k + b_k + c_k + \sigma)V_2 - a'_k S_k - b_k E_k - c_k I_k - \sigma N_k. \end{cases} \tag{2.9}$$

For system (2.9), it is obvious that

$$\begin{aligned} \frac{dV_1(t)}{dt} &\leq aN_0 - (a' + b + c + \delta)V_1, \\ \frac{dV_2(t)}{dt} &\leq a_k N_{0_k} - (a'_k + b_k + c_k + \sigma)V_2. \end{aligned} \tag{2.10}$$

By the properties of the Lyapunov function, we obtain the following conditions:

$$\begin{cases} \dfrac{dV_1}{dt} \leq aN_0 - (a' + b + c + \delta)V_1 \leq 0 \ \text{ for } \ V_1 \geq \dfrac{aN_0}{a' + b + c + \sigma}, \\ \dfrac{dV_2}{dt} \leq a_k N_{0_k} - (a'_k + b_k + c_k + \sigma)V_2 \leq 0 \ \text{ for } \ V_2 \geq \dfrac{a_k N_{0_k}}{a'_k + b_k + c_k + \sigma}. \end{cases} \tag{2.11}$$

From the conditions of (2.11), it follows that $\dfrac{dV(t)}{dt} \leq 0$, which means that Ω is a positively invariant and absorbing set.

From the above equations and conditions (2.9), we obtain the inequalities for V_1 and V_2:

$$\begin{aligned} 0 \leq V_1(t) &\leq \frac{aN_0}{a' + b + c + \delta} + e^{-(a' + b + c + \delta)t}\left(V_{0_1} - \frac{aN_0}{a' + b + c + \delta}\right), \\ 0 \leq V_2(t) &\leq \frac{a_k N_{0_k}}{a'_k + b_k + c_k + \sigma} + e^{-(a'_k + b_k + c_k + \sigma)t}\left(V_{0_2} - \frac{a_k N_{0_k}}{a'_k + b_k + c_k + \sigma}\right). \end{aligned}$$

For $t \longrightarrow +\infty$ we get

$$\begin{aligned} 0 \leq V_1(t) &\leq \frac{aN_0}{a' + b + c + \delta}, \\ 0 \leq V_2(t) &\leq \frac{a_k N_{0_k}}{a'_k + b_k + c_k + \sigma}, \end{aligned}$$

and we can conclude that Ω is an absorbing set. Indeed, the following inequalities

hold for $t \longrightarrow +\infty$:

$$\limsup_{t\to+\infty} V_1 \leq \frac{aN_0}{a' + b + c + \delta},$$
$$\limsup_{t\to+\infty} V_2 \leq \frac{a_k N_{0_k}}{a'_k + b_k + c_k + \sigma}.$$

Thus, Ω is positively invariant, and all solutions are bounded in interval $[0, \infty)$. $\square$

2.2.2 Equilibrium points

For the model, we study two equilibrium points for a system of differential equations (2.7):

1. Equilibrium without disease E_s;
2. Endemic equilibrium E_e.

Solving the following system of differential equations

$$\begin{cases} -\alpha S(t)I_k(t) + aN(t) - a'S(t) - dvS(t) &= 0 \\ \alpha S(t)I_k(t) + \mu R(t) - bE(t) - \beta E(t) &= 0, \\ \beta E(t) - cI(t) - \gamma I(t) &= 0, \\ \gamma I(t) - \delta R(t) - \mu R(t) + dvS(t) &= 0, \\ -\alpha_k S_k(t)I(t) + a_k N_k(t) - a'_k S_k(t) - \sigma S_k(t) &= 0, \\ \alpha_k S_k(t)I(t) - b_k E_k(t) - \beta_k E_k(t) - \sigma E_k(t) &= 0, \\ \beta_k E_k(t) - c_k I_k(t) - \sigma I_k(t) &= 0, \end{cases} \tag{2.12}$$

find two equilibrium points:

1. Equilibrium without disease $E_s = (\frac{a}{a'+dv}N_0, 0, 0, 0, \frac{a_k}{a'_k+dv}N_{0_k}, 0, 0)$, t .e. this is a solution to a system in which there are no disease cases in both populations;
2. Endemic equilibrium of system $E_e = (S^*, E^*, I^*, R^*, S^*_k, E^*_k, I^*_k)$, implying the presence of a disease and all subpopulations are present in population.

To find equilibrium, from the first equation of system (2.12) we get $S = \dfrac{aN_0}{\alpha I_k + a' + dv}$, from the third equation we get $E = \dfrac{c+\gamma}{\beta} I$ or $I = \dfrac{\beta}{c+\gamma} E$, then from the fourth equation: $R = \dfrac{\gamma}{\delta+\mu} I + \dfrac{dv}{\sigma+\mu} S$, from the fifth equation: $S_k = \dfrac{a_k N_{0_k}}{\alpha_k I + a'k + \sigma}$, from the sixth equation: $E_k = \dfrac{\alpha_k S_k}{b_k + \beta_k + \sigma} I$, from the seventh equation: $I_k = \dfrac{\beta_k E_k}{c_k + \sigma}$, from the second equation: $E = \dfrac{\alpha}{b+\beta} S I_k + \dfrac{\mu}{b+\beta} R$.

Substituting the first, third, fourth, fifth, sixth and seventh equations of system (2.12) into the second equation of the system, we obtain

$$E = \frac{aa_k\alpha\alpha_k\beta_k N_0 N_{0_k}(\gamma + c)(\delta + \mu)I + \mu a N_0(\gamma + c)K_1}{K_2(a_k\alpha\alpha_k\beta_k N_{0_k} I + (a' + dv)K_1)},$$

where

$$K_1 = (c_k + \sigma)(\beta_k + b_k + \sigma)(\alpha_k I + a'_k + \sigma),$$
$$K_2 = (b + \beta)(\delta + \mu)(c + \gamma) - \mu\gamma\beta.$$

Establishing equality with the third equation obtained in system (2.12), we get an equation of the second degree, which has two solutions, and the solution that satisfies the conditions is:

$$I = \frac{-(\beta a N_0\alpha_k(\alpha\beta_k a_k N_k(\delta + \mu) + \mu(c_k + \sigma)(\beta_k + b_k + \sigma)))}{2K_2(\alpha\alpha_k\beta_k a_k N_{k_0} + \alpha_k(a' + dv)(c_k + \sigma)(\beta_k + b_k + \sigma))} +$$
$$+ \frac{-(K_2(a' + dv)(c_k + \sigma)(\beta_k + b_k + \sigma)(a'_k + \sigma)) + \sqrt{\Delta}}{2K_2(\alpha\alpha_k\beta_k a_k N_{k_0} + \alpha_k(a' + dv)(c_k + \sigma)(\beta_k + b_k + \sigma))},$$

where

$$\begin{aligned}\Delta = {} & [K_2(a' + dv)(c_k + \sigma)(\beta_k + b_k + \sigma)(a'_k + \sigma) + \\ & + K_2(a' + dv)(c_k + \sigma)(\beta_k + b_k + \sigma)(a'_k + \sigma)]^2 - \\ & - 4K_2(\alpha\alpha_k\beta_k a_k N_{k_0} + \alpha_k(a' + dv)(c_k + \sigma)\times \\ & \times (\beta_k + b_k + \sigma))(\beta a N_0\mu(c_k + \sigma)(\beta_k + b_k + \sigma)(a'_k + \sigma)).\end{aligned}$$

Therefore, the endemic equilibrium of model (2.7) is defined as a vector

$E_e = (S^*, E^*, I^*, R^*, S_k^*, E_k^*, I_k^*)$ with components:

$$I^* = \frac{-(\beta a N_0 \alpha_k(\alpha\beta_k a_k N_k(\delta+\mu) + \mu(c_k+\sigma)(\beta_k+b_k+\sigma)))}{2K_2(\alpha\alpha_k\beta_k a_k N_{k_0} + \alpha_k(a'+dv)(c_k+\sigma)(\beta_k+b_k+\sigma))} +$$
$$+ \frac{-(K_2(a'+dv)(c_k+\sigma)(\beta_k+b_k+\sigma)(a_k'+\sigma)) + \sqrt{\Delta}}{2K_2(\alpha\alpha_k\beta_k a_k N_{k_0} + \alpha_k(a'+dv)(c_k+\sigma)(\beta_k+b_k+\sigma))},$$
$$S^* = \frac{aN_0}{\alpha I_k^* + a' + dv},$$
$$E^* = \frac{c+\gamma}{\beta} I^*,$$
$$R^* = \frac{\gamma}{\delta+\mu} I^* + \frac{dv}{\delta+\mu} S^*,$$
$$S_k^* = \frac{a_k N_{0_k}}{\alpha_k I^* + a_k'}\sigma,$$
$$E_k^* = \frac{\alpha_k}{b_k+\beta_k-\sigma} S_k^* I^*,$$
$$I_k^* = \frac{\beta_k}{c_k+\sigma} E_k^*.$$

Equilibrium E_e is an endemic point of the model, where all subgroups of two populations are represented.

2.2.3 Determining basic reproduction number R_0

Determine basic reproduction number R_0 for modified model $SEIRS_kE_kI_k$ presented above. This number is used to study the epidemic process evolution and can be interpreted as an average number of new malaria cases caused by one infected person in a fully susceptible population. To calculate R_0, we use a *method of next-generation matrix* described in $[29-32]$. For the presented model, the calculation of R_0 can be represented as follows:

$$\frac{dx}{dt} = F(x) - V(x),$$
$$x = (S, E, I, R, S_k, E_k, I_k)^T.$$

Using a next generation matrix method, the following calculations are required. First, we define matrices F and V:

$$\mathcal{F} = \begin{pmatrix} \alpha_k S_k(t) I(t) \\ 0 \\ \alpha S(t) I_k(t) \\ 0 \end{pmatrix}, \quad \mathcal{V}^+ = \begin{pmatrix} \mu R(t) \\ \beta E(t) \\ 0 \\ \beta_k E_k(t) \end{pmatrix}, \quad \mathcal{V}^- = \begin{pmatrix} -(b+\beta)E(t) \\ -(c+\gamma)I(t) \\ -(b_k+\beta_k)E_k(t) - \sigma E_k \\ -c_k I_k(t) - \sigma I_k(t) \end{pmatrix},$$

hence we get that

$$\mathcal{V} = \mathcal{V}^+ + \mathcal{V}^- = \begin{pmatrix} \mu R(t) - (b+\beta)E(t) \\ \beta E(t) - (c+\gamma)I(t) \\ -(b_k+\beta_k)E_k(t) - \sigma E_k \\ \beta_k E_k(t) - c_k I_k(t) - \sigma I_k \end{pmatrix}.$$

Define matrices

$$D\mathcal{F}(E_s) = \begin{pmatrix} 0 & \alpha_k S_k^0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \alpha S^0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$D\mathcal{V}(E_s) = \begin{pmatrix} -(b+\beta) & 0 & 0 & 0 \\ \beta & -(c+\gamma) & 0 & 0 \\ 0 & 0 & -(b_k+\beta_k+\sigma) & 0 \\ 0 & 0 & \beta_k & -(c_k+\sigma) \end{pmatrix}.$$

Hence,

$$F = \begin{bmatrix} 0 & \alpha_k S_k^0 \\ 0 & 0 \end{bmatrix}, \quad F' = \begin{bmatrix} 0 & \alpha S^0 \\ 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} -(b+\beta) & 0 \\ \beta & -(c+\gamma) \end{bmatrix}, \quad V' = \begin{bmatrix} -(b_k+\beta_k+\sigma) & 0 \\ \beta_k & -(c_k+\sigma) \end{bmatrix}.$$

Calculate R_0 using formula $R_0 = \rho(-FV^{-1})$, where

$$V^{-1} = \frac{1}{det(V)} t_{(com(V))},$$

and

$$det(V) = (b+\beta)(c+\gamma), \quad t_{(com(V))} = \begin{bmatrix} -(c+\gamma) & 0 \\ -\beta & -(b+\beta) \end{bmatrix}.$$

Substituting $det(V)$ and $t_{(com(V))}$ into expression V^{-1}, we get

$$V^{-1} = \frac{1}{(b+\beta)(c+\gamma)} \begin{bmatrix} -(c+\gamma) & 0 \\ -\beta & -(b+\beta) \end{bmatrix},$$

$$(V')^{-1} = \frac{1}{(b_k+\beta_k+\sigma)(c_k+\sigma)} \begin{bmatrix} -(c_k+\sigma) & 0 \\ -\beta_k & -(b_k+\beta_k+\sigma) \end{bmatrix}.$$

These formulas are valid:

$$FV^{-1} = \begin{bmatrix} -\frac{\alpha_k \beta S_k^0}{(b+\beta)(c+\gamma)} & -\frac{\alpha_k S_k^0}{c+\gamma} \\ 0 & 0 \end{bmatrix},$$

$$FV'^{-1} = \begin{bmatrix} -\frac{\alpha\beta_k S^0)}{(c_k+\sigma)(b_k+\beta_k+\sigma)} & -\frac{\alpha S^0}{(c_k+\sigma)} \\ 0 & 0 \end{bmatrix},$$

calculate R_h and R_k:

$$R_h = \rho(-FV^{-1}) = \frac{\alpha_k \beta S_k^0}{(b+\beta)(c+\gamma)}, \quad R_k = \rho(-FV'^{-1}) = \frac{\alpha\beta_k S^0}{(c_k+\sigma)(b_k+\beta_k+\sigma)},$$

from which we obtain the basic reproduction number R_0 in the form:

$$R_0 = R_h \times R_k = \frac{\alpha_k \beta S_k^0 \alpha\beta_k S^0}{c_k+\sigma)(b_k+\beta_k+\sigma)(b+\beta)(c+\gamma)},$$

where $(S^0, S_k^0) = (\frac{a}{a'+dv}N_0, \frac{a_k}{a'_k+\sigma}N_{0_k})$, and as a result write the final formula for R_0:

$$R_0 = \frac{\alpha\beta\alpha_k\beta_k a a_k N_0 N_{0_k}}{(a'_k+\sigma)(c_k+\sigma)(a'+dv)(b+\beta)(c+\gamma)(b_k+\beta_k+\sigma)}.$$

R_0 gives information about the disease course. If $R_0 \leq 1$, the number of infected people will decrease, and the disease will eventually pass. If $R_0 \geq 1$, the number of infected people increases, the disease can spread to the entire population and become endemic. Numerical analysis will show how the disease proceeds in the population at different values of R_0.

2.2.4 Study of equilibrium stability

First, we analyze the stability of equilibrium without disease using the system of equations (2.7) using basic reproductive number R_0.

Theorem 2.5. *Disease-free equilibrium E_s is locally asymptotically stable if $R_0 \leq 1$ and $\frac{B_1B_2B_3+B_1B_5}{B_1^2B_4+B_3^2} > 1$, and unstable if $R_0 > 1$.*

Remark 2.1. *Expressions for B_1, B_2, B_3, B_4 and B_5 are given in the proof.*

Proof. The Jacobi matrix of system (2.7) is written as

$$J(S, E, I, R, S_k, E_k, I_k) =$$

$$\begin{pmatrix} -\alpha I_k - a' - dv & 0 & 0 & 0 & 0 & 0 & -\alpha S \\ \alpha I_k & -b-\beta & 0 & \mu & 0 & 0 & \alpha S \\ 0 & \beta & -c-\gamma & 0 & 0 & 0 & 0 \\ dv & 0 & \gamma & -\delta-\mu & 0 & 0 & 0 \\ 0 & 0 & -\alpha_k S_k & 0 & -\alpha_k I - a'_k - \sigma & 0 & 0 \\ 0 & 0 & \alpha_k S_k & 0 & \alpha_k I & -b_k-\beta_k-\sigma & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_k & -c_k-\sigma \end{pmatrix}.$$

The Jacobi matrix at disease-free equilibrium point E_s is equal to

$$J(E_s) = \begin{pmatrix} -a' - dv & 0 & 0 & 0 & 0 & 0 & -\alpha\frac{aN_0}{a'+dv} \\ 0 & -b-\beta & 0 & \mu & 0 & 0 & \alpha\frac{aN_0}{a'+dv} \\ 0 & \beta & -c-\gamma & 0 & 0 & 0 & 0 \\ dv & 0 & \gamma & -\delta-\mu & 0 & 0 & 0 \\ 0 & 0 & -\alpha_k\frac{a_kN_{0_k}}{a'_k+\sigma} & 0 & -a'_k-\sigma & 0 & 0 \\ 0 & 0 & \alpha_k\frac{a_kN_{0_k}}{a'_k+\sigma} & 0 & 0 & -(b_k+\beta_k+\sigma) & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_k & -c_k-\sigma \end{pmatrix}.$$

Let's find the eigenvalues of this matrix by equating its determinant to zero, that is,

$$\begin{vmatrix} -a' - dv - \lambda & 0 & 0 & 0 & 0 & 0 & -\alpha\frac{aN_0}{a'+dv} \\ 0 & -b-\beta-\lambda & 0 & \mu & 0 & 0 & \alpha\frac{aN_0}{a'+dv} \\ 0 & \beta & -c-\gamma-\lambda & 0 & 0 & 0 & 0 \\ dv & 0 & \gamma & -\delta-\mu-\lambda & 0 & 0 & 0 \\ 0 & 0 & -\alpha_k\frac{a_kN_{0_k}}{a'_k-\sigma} & 0 & -a'_k-\sigma-\lambda & 0 & 0 \\ 0 & 0 & \alpha_k\frac{a_kN_{0_k}}{a'_k+\sigma} & 0 & 0 & -(b_k+\beta_k+\sigma)-\lambda & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_k & -c_k-\sigma-\lambda \end{vmatrix}$$

we obtain the following characteristic equation:

$$\lambda^7 + B_1\lambda^6 + B_2\lambda^5 + B_3\lambda^4 + B_4\lambda^3 + B_5\lambda^2 + B_6\lambda + B_7 = 0,$$

where

$$B_1 = \beta_k + b_k + c_k + 3\sigma + a'_k + \gamma + c + \delta + \mu + a' + dv + b + \beta,$$

$$B_2 = (\beta_k + b_k + \sigma)(c_k + \sigma) + (b_k + \beta_k + c_k + 2\sigma)(a'_k + \sigma) + (\gamma + c + \delta + \mu +$$
$$+ a' + dv + \beta + b)(\beta_k + b_k + c_k + 3\sigma + a'_k) + (a' + dv)(\beta + b) +$$
$$+ (a' + dv + \beta + b)(\gamma + c + \delta + \mu) + (\gamma + c)(\delta + \mu),$$

$$B_3 = (a'_k + \sigma)(\beta_k + b_k + \sigma)(c_k + \sigma) + (\gamma + c + \delta + \mu + a' + dv + \beta + b)$$
$$((\beta_k + b_k + \sigma)(c_k + \sigma) + (b_k + \beta_k + c_k + 2\sigma)(a'_k + \sigma)) + ((a' + dv)(\beta + b) +$$
$$+ (a' + dv + \beta + b)(\gamma + c + \delta + \mu) +$$
$$+ (\gamma + c)(\delta + \mu))(\beta_k + b_k + c_k + 3\sigma + a'_k) + ((a' + dv)(\beta + b)(\gamma + c + \delta + \mu) +$$
$$+ (\gamma + c)(\delta + \mu)(a' + dv + \beta + b)) + \beta\gamma\mu,$$

$$B_4 = (\gamma + c + \delta + \mu + a' + dv + \beta + b)(a'_k + \sigma)(\beta_k + b_k + \sigma)(c_k + \sigma) +$$
$$+ ((a' + dv)(\beta + b) + (a' + dv + \beta + b)(\gamma + c + \delta + \mu) +$$
$$+ (\gamma + c)(\delta + \mu))((\beta_k + b_k + \sigma)(c_k + \sigma) + (b_k + \beta_k + c_k + 2\sigma)(a'_k + \sigma)) +$$
$$+ (a' + dv)(\beta + b)(\gamma + c + \delta + \mu) + (\gamma + c)(\delta + \mu)(a' + dv + \beta + b) +$$
$$+ ((a' + dv)(\beta + b) + (a' + dv + \beta + b)(\gamma + c + \delta + \mu) +$$
$$+ (\gamma + c)(\delta + \mu))(\beta_k + b_k + c_k + 3\sigma + a'_k) + (a' + dv)(\beta + b)(\gamma + c)(\delta + \mu) -$$
$$- \frac{\alpha\beta\alpha_k\beta_k a a_k N_0 N_{0_k}}{(a'_k + \sigma)(a' + dv)} + \beta\gamma\mu(b_k + \beta_k + c_k + 2\sigma) + \beta\gamma\mu(a' + a_k + dv + \sigma),$$

$$B_5 = (a'_k + \sigma)(\beta_k + b_k + \sigma)(c_k + \sigma)((a' + dv)(\beta + b) + (a' + dv + \beta + b)$$
$$(\gamma + c + \delta + \mu) + (\gamma + c)(\delta + \mu)) + ((a' + dv)(\beta + b)(\gamma + c + \delta + \mu) +$$
$$+ (\gamma + c)(\delta + \mu)(a' + dv + \beta + b))((\beta_k + b_k + \sigma)(c_k + \sigma) +$$
$$+ (a'_k + \sigma)(\beta_k + b_k + c_k + 2\sigma)) + (a' + dv)(b + \beta)(c + \gamma)(\delta + \mu)$$
$$(b_k + \beta_k + c_k + 3\sigma + a'_k) - \frac{2\alpha\beta\alpha_k\mu a a_k dv N_0 N_{0_k}}{(a'_k + \sigma)(a' + dv)} -$$
$$- \frac{\alpha\beta\alpha_k\beta_k a a_k N_0 N_{0_k}}{(a'_k + \sigma)(a' + dv)}(\delta + \mu) + \beta\gamma\mu(b_k + \beta_k + \sigma)(c_k + \sigma) - (a' + a_k + dv + \sigma)$$
$$(\frac{\alpha\beta\alpha_k\beta_k a a_k N_0 N_{0_k}}{(a'_k + \sigma)(a' + dv)} + \beta\gamma\mu(b_k + \beta_k + c_k + 2\sigma) + \beta\gamma\mu(a' + dv)(a'_k + \sigma),$$

$$B_6 = ((a' + dv)(b + \beta)(c + \gamma + \delta + \mu) + (c + \gamma)(\delta + \mu)(a' + dv + b + \beta))$$
$$((a'_k + \sigma)(\beta_k + b_k + \sigma)(c_k + \sigma) + (\beta_k + b_k + \sigma)(c_k + \sigma) + (a'_k + \sigma)$$
$$(\beta_k + b_k + c_k + 2\sigma))(a' + dv)(\beta + b)(\gamma + c)(\delta + \mu) -$$
$$- \frac{\alpha\beta\alpha_k\mu a a_k dv N_0 N_{0_k}}{(a'_k + \sigma)(a' + dv)}(2c_k + a'_k + \beta_k + b_k + 4\sigma)$$

.

$$
\begin{aligned}
&- \frac{\alpha\beta\alpha_k\mu a a_k dv N_0 N_{0_k}}{(a'_k+\sigma)(a'+dv)}(2c_k + a'_k + \beta_k + b_k + 4\sigma) - \\
&- (a' - a_k + dv + \sigma)\frac{\alpha\beta\alpha_k\beta_k a a_k N_0 N_{0_k}}{(a'_k+\sigma)(a'+dv)}(\delta+\mu) + \beta\gamma\mu(b_k+\beta_k+\sigma)(c_k+\sigma) - \\
&- (a'_k+\sigma)(a'+dv)\frac{\alpha\beta\alpha_k\beta_k a a_k N_0 N_{0_k}}{(a'_k+\sigma)(a'+dv)} + \beta\gamma\mu(b_k+\beta_k+c_k+2\sigma), \\
B_7 = &(a'+dv)(b+\beta)(c+\gamma)(\delta+\mu)(a'_k+\sigma)(\beta_k+b_k+\sigma)(c_k+\sigma) - \\
&- (a'_k+\sigma)(a'+dv)\frac{\alpha\beta\alpha_k\beta_k a a_k N_0 N_{0_k}}{(a'_k+\sigma)(a'+dv)}(\delta+\mu) + \beta\gamma\mu(b_k+\beta_k+\sigma)(c_k+\sigma) - \\
&- \frac{\alpha\beta\alpha_k\mu a a_k dv N_0 N_{0_k}}{(a'_k+\sigma)(a'+dv)}(c_k+\sigma)(a'_k+\beta_k+b_k+2\sigma).
\end{aligned}
$$

The characteristic equation can have seven roots, which can be obtained by solving the following equation:

$$\lambda^7 + B_1\lambda^6 + B_2\lambda^5 + B_3\lambda^4 + B_4\lambda^3 + B_5\lambda^2 + B_6\lambda + B_7 = 0.$$

It is impossible to write the solutions explicitly, so to determine the nature of the stability of equilibrium point E_s, we use the Routh-Hurwitz criterion to study the stability. To do this, we write an auxiliary matrix

$$
\begin{vmatrix}
1 & B_2 & B_4 & B_6 & 0 & 0 \\
B_1 & B_3 & B_5 & B_7 & 0 & 0 \\
\frac{B_1B_2 - B_3}{B_1} & \frac{B_1B_4 - B_5}{B_1} & \frac{B_1B_6 - B_7}{B_1} & 0 & 0 & 0 \\
B_3 - \frac{B_1(B_1B_4 - B_5)}{B_1B_2 - B_3} & B_5 - \frac{B_1(B_1B_6 - B_7)}{B_1B_2 - B_3} & B_7 & 0 & 0 & 0 \\
B'_1 & B'_2 & 0 & 0 & 0 & 0 \\
B'_3 & B_7 & 0 & 0 & 0 & 0 \\
\frac{B'_3B'_2 - B'_1B_7}{B'_3} & 0 & 0 & 0 & 0 & 0 \\
B_7 & 0 & 0 & 0 & 0 & 0,
\end{vmatrix}.
$$

where

$$
\begin{aligned}
B'_1 &= \frac{B_1B_4 - B_5}{B_1} - \frac{(B_1B_2 - B_3)(B_5(B_1B_2 - B_3) - B_1(B_1B_6 - B_7))}{B_1(B_3(B_1B_2 - B_3) - B_1(B_1B_4 - B_5))}, \\
B'_2 &= \frac{B_1B_6 - B_7}{B_1} - \frac{B_7(B_1B_2 - B_3)^2}{B_1(B_3(B_1B_2 - B_3) - B_1(B_1B_4 - B_5))}, \\
B'_3 &= B_5 - \frac{B_1(B_1B_6 - B_7)}{B_1B_2 - B_3} - \frac{B_3(B_1B_2 - B_3) - B_1(B_1B_4 - B_5)}{B_1B_2 - B_3}\frac{B'_2}{B'_1}.
\end{aligned}
$$

Applying the Routh-Hurwitz criterion, we obtain that system (2.7) is asymptotically stable at equilibrium E_s if these inequalities are satisfied:

$$\begin{aligned}
B_1 &> 0,\\
B_7 &> 0,\\
\frac{B_1B_2-B_3}{B_1} &> 0,\\
B_3-\frac{B_1(B_1B_4-B_5)}{B_1B_2-B_3} &> 0,\\
\frac{B_1B_4-B_5}{B_1}-\frac{(B_1B_2-B_3)(B_5(B_1B_2-B_3)-B_1(B_1B_6-B_7))}{B_1(B_3(B_1B_2-B_3)-B_1(B_1B_4-B_5))} &> 0,\\
\frac{B_1B_6-B_7}{B_1}-\frac{B_7(B_1B_2-B_3)^2}{B_1(B_3(B_1B_2-B_3)-B_1(B_1B_4-B_5))} &> 0,\\
B_5-\frac{B_1(B_1B_6-B_7)}{B_1B_2-B_3}-\frac{B_3(B_1B_2-B_3)-B_1(B_1B_4-B_5)}{B_1B_2-B_3}\frac{B_2'}{B_1'} &> 0,\\
\frac{B_3'B_2'-B_1'B_7}{B_3'} &> 0.
\end{aligned}$$

Then from $\frac{B_1B_2-B_3}{B_1}>0$ and $B_1>0$ it follows that $B_1B_2-B_3>0$. The fourth inequality is equivalent to $B_3(B_1B_2-B_3)-B_1(B_1B_4-B_5)>0$, or $B_1B_2-B_3>0$. The fifth inequality is equivalent to $B_1(B_1B_4-B_5)(B_3(B_1B_2-B_3)-B_1(B_1B_4-B_5))-B_1(B_1B_2-B_3)(B_5(B_1B_2-B_3)-B_1(B_1B_2-B_3)-B_1B_6-B_7))>0$, or $B_1^2(B_3(B_1B_2-B_3)-B_1(B_1B_4-B_5)>0$. The sixth inequality is equivalent to $B_1(B_1B_6-B_7)(B_3(B_1B_2-B_3)-B_1(B_1B_4-B_5))-B_1B_7(B_1B_2-B_3)^2>0$, or $B_1'>0$. The seventh inequality is equivalent to $B_5B_1'(B_1B_2-B_3)-B_1B_1'(B_1B_6-B_7)-B_2'(B_3(B_1B_2-B_3)-B_1(B_1B_4-B_5))>0$. Then the last inequality can be simplified as $B_3'B_2'-B_1'B_7>0$, or $B_3'>0$.

Therefore, we get the system:

$$\begin{aligned}
B_1 &> 0,\\
B_7 &> 0,\\
B_1B_2 - B_3 &> 0,\\
B_3(B_1B_2 - B_3) - B_1(B_1B_4 - B_5) &> 0,\\
B_1(B_1B_4 - B_5)(B_3(B_1B_2 - B_3) - B_1(B_1B_4 - B_5))-&\\
-B_1(B_1B_2 - B_3)(B_5(B_1B_2 - B_3) - B_1(B - 1B_6 - B_7)) &> 0,\\
B_1(B_1B_6 - B_7)(B_3(B_1B_2 - B_3) - B_1(B_1B_4 - B_5)) - B_1B_7(B_1B_2 - B_3)^2 &> 0,\\
B_5B_1'(B_1B_2 - B_3) - B_1B_1'(B_1B_6 - B_7) - B_2'(B_3(B_1B_2 - B_3)-&\\
-B_1(B_1B_4 - B_5)) &> 0,\\
B_3'B_2' - B_1'B_7 &> 0,
\end{aligned}$$

then seven eigenvalues have negative real parts, which follows from the Routh-Hurwitz criterion. Thus, all eigenvalues of the characteristic equation have negative real parts if and only if $R_0 < 1$ and $B_1B_2B_3+B_1B_5 > B_1^2B_4+B_3^2$, i.e. $\frac{B_1B_2B_3+B_1B_5}{B_1^2B_4+B_3^2} > 1$, then the disease-free equilibrium E_s is locally asymptotically stable. □

Theorem 2.6. *Endemic equilibrium point E_e is locally asymptotically stable if $R_0 > 1$ and $\frac{D_1D_2D_3+D_1D_5}{D_1^2D_4+D_3^2} > 1$.*

Remark 2.2. *Expressions for D_1, D_2, D_3, D_4 and D_5 are given in the proof.*

Proof. The Jacobi matrix of system (2.7) is written as:
$J(S, E, I, R, S_k, E_k, I_k) =$

$$\begin{pmatrix}
-\alpha I_k - a' - dv & 0 & 0 & 0 & 0 & 0 & -\alpha S\\
\alpha I_k & -b-\beta & 0 & \mu & 0 & 0 & \alpha S\\
0 & \beta & -c-\gamma & 0 & 0 & 0 & 0\\
dv & 0 & \gamma & -\delta-\mu & 0 & 0 & 0\\
0 & 0 & -\alpha_k S_k & 0 & \alpha_k I - a_k' - \sigma & 0 & 0\\
0 & 0 & \alpha_k S_k & 0 & \alpha_k I & -(b_k+\beta_k+\sigma) & 0\\
0 & 0 & 0 & 0 & 0 & \beta_k & -c_k-\sigma
\end{pmatrix}.$$

The Jacobi matrix at endemic equilibrium $E_e = (S^*, E^*, I^*, R^*, S_k^*, E_k^*, I_k^*)$ can be written as

$$J(E_e) =$$

$$\begin{pmatrix} -\alpha I_k^* - a' - dv & 0 & 0 & 0 & 0 & 0 & -\alpha S^* \\ \alpha I_k^* & -b-\beta & 0 & \mu & 0 & 0 & \alpha S^* \\ 0 & \beta & -c-\gamma & 0 & 0 & 0 & 0 \\ dv & 0 & \gamma & -\delta-\mu & 0 & 0 & 0 \\ 0 & 0 & -\alpha_k S_k^* & 0 & -\alpha_k I^* - a_k' - \sigma & 0 & 0 \\ 0 & 0 & \alpha_k S_k^* & 0 & \alpha_k I^* & -(b_k+\beta_k+\sigma) & 0 \\ 0 & 0 & 0 & 0 & 0 & \beta_k & -c_k-\sigma \end{pmatrix}.$$

Let us find the eigenvalues of this matrix, equating its determinant to zero, we obtain the following characteristic equation:

$$\lambda^7 + D_1\lambda^6 + D_2\lambda^5 + D_3\lambda^4 + D_4\lambda^3 + D_5\lambda^2 + D_6\lambda + D_7 = 0,$$

where

$$\begin{aligned}
D_1 &= (\beta + b + \gamma + c + \alpha_k I^* + a_k' + 2\sigma + \beta_k + b_k + c_k + \sigma + \alpha I_k^* + a' + dv),\\
D_2 &= (\beta_k + b_k + \sigma)(\beta + b + \gamma + c + \alpha_k I^* + a_k' + \sigma) +\\
&\quad + (\beta + b)(\gamma + c) + (\beta + b + \gamma + c)(\delta + \mu + \alpha_k I^* + a_k' + \sigma) +\\
&\quad + (\delta + \mu)(\alpha_k I^* + a_k' + \sigma) + (\beta_k + b_k + \sigma)(\beta + b + \gamma + c + \alpha_k I^* + a_k' +\\
&\quad + 2\sigma + \beta_k + b_k)(c_k + \sigma + \alpha I_k^* + a' + dv) + (c_k + \sigma)(\alpha_k I^* + a' + dv),\\
D_3 &= (\beta_k + b_k + \sigma)((\beta + b)(\gamma + c) + (\beta + b + \gamma + c)(\delta + \mu + \alpha_k I^* + a_k' + \sigma) +\\
&\quad + (\delta + \mu)(\alpha_k I^* + a_k' + \sigma) + \beta\alpha\gamma) + (c_k + \sigma + \alpha I_k^* + a' + dv)\\
&\quad ((\beta_k + b_k + \sigma)(\beta + b + \gamma + c + \alpha_k I^* + a_k' + \sigma) + (\beta + b)(\gamma + c) +\\
&\quad + (\beta + b + \gamma + c)(\delta + \mu + \alpha_k I^* + a_k' + \sigma) + (\delta + \mu)(\alpha_k I^* + a_k' + \sigma)) +\\
&\quad + (\beta + b + \gamma + c + \alpha_k I^* + a_k' + 2\sigma + \beta_k + b_k)((c_k + \sigma)(\alpha_k I^* + a' + dv)),\\
D_4 &= \beta\alpha\beta_k\alpha_k S^{*2} + \beta\gamma\mu\beta_k + \beta\gamma\mu b_k + 2\beta\gamma\mu\sigma + \beta\gamma\mu\alpha_k I^* + \beta\gamma\mu a_k' +\\
&\quad + (\beta_k + b_k + \sigma)((\beta + b)(\gamma + c)(\delta + \mu + \alpha_k I^* + a_k' + \sigma) +\\
&\quad + (\beta + b + \gamma + c)(\delta + \mu)(\alpha_k I^* + a_k' + \sigma)) +\\
&\quad + (\beta + b)(\gamma + c)(\delta + \mu)(\alpha_k I^* + a_k' + \sigma) + (c_k + \sigma + \alpha I_k^* + a' + dv)\\
&\quad ((\beta_k + b_k + \sigma)((\beta + b)(\gamma + c) + (\beta + b + \gamma + c)(\delta + \mu + \alpha_k I^* + a_k' + \sigma) +\\
&\quad + (\delta + \mu) + (\alpha_k I^* + a_k' + \sigma) + \beta\alpha\gamma)) + ((\beta_k + b_k + \sigma)(\beta + b + \gamma + c +
\end{aligned}$$

$$+\alpha_k I^* + a'_k + \sigma)+$$
$$+(\beta+b)(\gamma+c)+(\beta+b+\gamma+c)(\delta+\mu+\alpha_k I^*+a'_k+\sigma)+$$
$$+(\delta+\mu)(\alpha_k I^*+a'_k+\sigma))((c_k+\sigma)(\alpha_k I^*+a'+dv)),$$

$$D_5=(\beta_k+b_k+\sigma)(\beta+b)(\gamma+c)(\delta+\mu)(\alpha_k I^*+a'_k+\sigma)-\beta\alpha S^*\beta_k\alpha_k^2 S_k^* I^*+$$
$$+\beta\alpha S^{*2} beta_k\alpha_k(\alpha_k I^*+a'_k+\sigma)+\beta\gamma\mu(\beta_k+b_k+\sigma)(\alpha_k I^*+a'_k+\sigma)+$$
$$+(c_k+\sigma+\alpha I_k^*+a'+dv)(\beta\alpha\beta_k\alpha_k S^{*2}+\beta\gamma\mu\beta_k+\beta\gamma\mu b_k+2\beta\gamma\mu\sigma+$$
$$+\beta\gamma\mu\alpha_k I^*+\beta\gamma\mu a'_k+(\beta_k+b_k+\sigma)((\beta+b)(\gamma+c)(\delta+\mu+\alpha_k I^*+$$
$$+a'_k+\sigma)+(\beta+b+\gamma+c)(\delta+\mu)(\alpha_k I^*+a'_k+\sigma))+(\beta+b)(\gamma+c)$$
$$(\delta+\mu)(\alpha_k I^*+a'_k+\sigma))+((\beta_k+b_k+\sigma)((\beta+b)(\gamma+c)+$$
$$+(\beta+b+\gamma+c)(\delta+\mu+\alpha_k I^*+a'_k+\sigma)+(\delta+\mu)(\alpha_k I^*+a'_k+\sigma)+\beta\alpha\gamma))$$
$$((c_k+\sigma)(\alpha_k I^*+a'+dv))+\alpha^2\beta\alpha_k\beta_k S_k^* S^* I_k^*.$$

$$D_6=((\beta_k+b_k+\sigma)(\beta+b)(\gamma+c)(\delta+\mu)(\alpha_k I^*+a'_k+\sigma)-\beta\alpha S^*\beta_k\alpha_k^2 S_k^* I^*+$$
$$+\beta\alpha S^{*2} beta_k\alpha_k(\alpha_k I^*+a'_k+\sigma)+\beta\gamma\mu(\beta_k+b_k+\sigma)(\alpha_k I^*+a'_k+\sigma))$$
$$(c_k+\sigma+\alpha I_k^*+a'+dv)+((c_k+\sigma)(\alpha_k I^*+a'+dv))((\beta_k+b_k+\sigma)(\beta+b)$$
$$(\gamma+c)(\delta+\mu)(\alpha_k I^*+a'_k+\sigma)-\beta\alpha S^*\beta_k\alpha_k^2 S_k^* I^*+$$
$$+\beta\alpha S^{*2} beta_k\alpha_k(\alpha_k I^*+a'_k+\sigma)+\beta\gamma\mu(\beta_k+b_k+\sigma)(\alpha_k I^*+a'_k+\sigma))+$$
$$+\alpha\beta\alpha_k\beta_k S_k^* S^*(\alpha_k I^*+a'_k+$$
$$+\sigma+\mu dv+\alpha I_k^*(\alpha+\mu)+\alpha_k I^*\alpha I_k^*),$$

$$D_7=((\beta_k+b_k+\sigma)(\beta+b)(\gamma+c)(\delta+\mu)(\alpha_k I^*+a'_k+\sigma)-\beta\alpha S^*\beta_k\alpha_k^2 S_k^* I^*+$$
$$+\beta\alpha S^{*2} beta_k\alpha_k(\alpha_k I^*+a'_k+\sigma)+\beta\gamma\mu(\beta_k+b_k+\sigma)(\alpha_k I^*+a'_k+\sigma))$$
$$((c_k+\sigma)(\alpha_k I^*+a'+dv))+\alpha\beta\alpha_k^2\beta_k\mu dv I^* S_k^* S^*+\alpha^2\beta\alpha_k^2\beta_k I^* S_k^* S^* I_k^*(\alpha+\mu)+$$
$$+\alpha\beta\alpha_k\beta_k S_k^* S^*(\alpha_k I^*+a'_k+\sigma)(\mu dv+\alpha I_k^*(\alpha+\mu)).$$

Matrix eigenvalues are solutions of the characteristic equation. The equation has seven roots. We use the Routh-Hurwitz criterion.

We write an auxiliary matrix

$$\begin{vmatrix} 1 & D_2 & D_4 & D_6 & 0 & 0 \\ D_1 & D_3 & D_5 & D_7 & 0 & 0 \\ \frac{D_1D_2-D_3}{D_1} & \frac{D_1D_4-D_5}{D_1} & \frac{D_1D_6-D_7}{D_1} & 0 & 0 & 0 \\ D_3-\frac{D_1(D_1D_4-D_5)}{D_1D_2-D_3} & D_5-\frac{D_1(D_1D_6-D_7)}{D_1D_2-D_3} & D_7 & 0 & 0 & 0 \\ D_1' & D_2' & 0 & 0 & 0 & 0 \\ D_3' & D_7 & 0 & 0 & 0 & 0 \\ \frac{D_3'D_2'-D_1'D_7}{D_3'} & 0 & 0 & 0 & 0 & 0 \\ D_7 & 0 & 0 & 0 & 0 & 0, \end{vmatrix},$$

where

$$D_1' = \frac{D_1D_4-D_5}{D_1} - \frac{(D_1D_2-D_3)(D_5(D_1D_2-D_3)-D_1(D_1D_6-D_7))}{D_1(D_3(D_1D_2-D_3)-D_1(D_1D_4-D_5))},$$
$$D_2' = \frac{D_1D_6-D_7}{D_1} - \frac{D_7(D_1D_2-D_3)^2}{D_1(D_3(D_1D_2-D_3)-D_1(D_1D_4-D_5))},$$
$$D_3' = D_5 - \frac{D_1(D_1D_6-D_7)}{D_1D_2-D_3} - \frac{D_3(D_1D_2-D_3)-D_1(D_1D_4-D_5)}{D_1D_2-D_3}\frac{D_2'}{D_1'}.$$

Applying the Routh-Hurwitz criterion, we obtain that system (2.7) is asymptotically stable at equilibrium point E_e if these inequalities are satisfied:

$$D_1 > 0,$$
$$D_7 > 0,$$
$$\frac{D_1D_2-D_3}{D_1} > 0,$$
$$D_3 - \frac{D_1(D_1D_4-D_5)}{D_1D_2-D_3} > 0,$$
$$\frac{D_1D_4-D_5}{D_1} - \frac{(D_1D_2-D_3)(D_5(D_1D_2-D_3)-D_1(D_1D_6-D_7))}{D_1(D_3(D_1D_2-D_3)-D_1(D_1D_4-D_5))} > 0,$$
$$\frac{D_1D_6-D_7}{D_1} - \frac{D_7(D_1D_2-D_3)^2}{D_1(D_3(D_1D_2-D_3)-D_1(D_1D_4-D_5))} > 0,$$
$$D_5 - \frac{D_1(D_1D_6-D_7)}{D_1D_2-D_3} - \frac{D_3(D_1D_2-D_3)-D_1(D_1D_4-D_5)}{D_1D_2-D_3}\frac{D_2'}{D_1'} > 0,$$
$$\frac{D_3'D_2'-D_1'D_7}{D_3'} > 0.$$

It follows from $\frac{D_1D_2-D_3}{D_1} > 0$ and $D_1 > 0$ that $D_1D_2 - D_3 > 0$. The fourth inequality is equivalent to $D_3(D_1D_2 - D_3) - D_1(D_1D_4 - D_5) > 0$, or $D_1D_2 -$

$D_3 > 0$. The fifth inequality is equivalent to $(D_1D_4 - D_5)(D_3(D_1D_2 - D_3) - D_1(D_1D_4 - D_5)) - (D_1D_2 - D_3)(D_5(D_1D_2 - D_3) - D_1(D_1D_6 - D_7)) > 0$, or $D_1(D_3(D_1D_2 - D_3) - (D_1D_4 - D_5)) > 0$. The sixth inequality is equivalent to $(D_1D_6 - D_7)(D_3(D_1D_2 - D_3) - D_1(D_1D_4 - D_5)) - D_7(D_1D_2 - D_3)^2 > 0$, or $D_1(D_3(D_1D_2 - D_3) - (D_1D_4 - D_5)) > 0$. The seventh inequality is equivalent to $D_5D_1'(D_1D_2 - D_3) - D_1D_1'(D_1D_6 - D_7) - D_2'(D_3(D_1D_2 - D_3) - D_1(D_1D_4 - D_5)) > 0$, or $D_1' > 0$. Then the last inequality can be simplified as $D_3'D_2' - D_1'D_7 > 0$, or $D_3' > 0$.

Therefore, we get the system:

$$
\begin{aligned}
D_1 &> 0,\\
D_7 &> 0,\\
D_1D_2 - D_3 &> 0,\\
D_3(D_1D_2 - D_3) - D_1(D_1D_4 - D_5) &> 0,\\
D_1(D_1D_4 - D_5)(D_3(D_1D_2 - D_3) - D_1(D_1D_4 - D_5)) &-\\
-D_1(D_1D_2 - D_3)(D_5(D_1D_2 - D_3) - D_1(D_1D_6 - D_7)) &> 0,\\
D_1(D_1D_6 - D_7)(D_3(D_1D_2 - D_3) - D_1(D_1D_4 - D_5)) - D_1D_7(D_1D_2 - D_3)^2 &> 0,\\
D_5D_1'(D_1D_2 - D_3) - D_1D_1'(D_1D_6 - D_7) - D_2'(D_3(D_1D_2 - D_3) &-\\
-D_1(D_1D_4 - D_5)) &> 0\\
D_3'D_2' - D_1'D_7 &> 0,
\end{aligned}
$$

Seven eigenvalues have negative real parts if they satisfy the Routh-Hurwitz criterion. Thus, all eigenvalues of a characteristic equation have negative real parts if and only if $R_0 > 1$ and $D_3D_1D_2 + D_1D_5 > D_3^2 + D_1^2D_4$, which is true when $\frac{D_1D_2D_3 + D_1D_5}{D_1^2D_4 + D_3^2} > 1$, then endemic equilibrium E_e is locally asymptotically stable. □

2.2.5 Numerical simulation

Numerical modeling allows us to better understand the dynamics of the malaria epidemic. Let us study the dynamics of development of each population subgroup depending on the disease severity. In this part, we will focus on the simulation parameters associated with vaccination by presenting several graphical representations of the disease dynamics with different values of the parameters and different values of R_0. Computer simulation is carried out using the *Matlab* software. The parameters used for numerical simulation are presented in Tables 2.4 and 2.5.

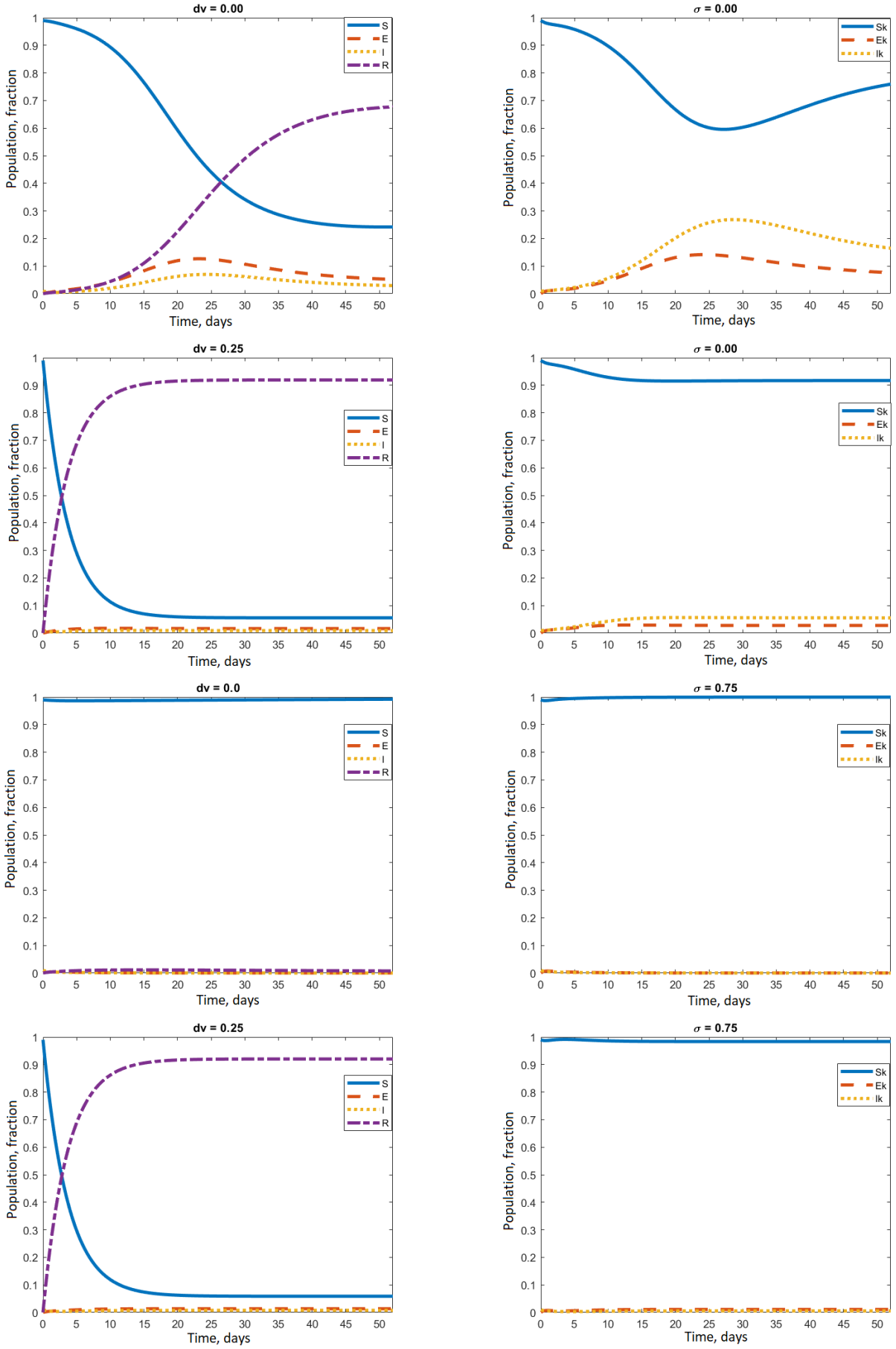

Figure 2.6: Epidemic process for different values of R_0 ($R_0 = 7.26$ and $R_0 = 0.32$).

Table 2.4: Parameters for the simulation, which results are presented in Fig. 2.6.

α	α_k	β	β_k	γ	μ	a	a'	a_k	a'_k	b	b_k	c	c_k	d	σ	dv	R_0
In Fig. 2.6 (first set of parameters)																	
0.72	2.0	0.5	0.5	0.5	0.01	0.8	0.01	0.4	0.2	0.2	0.1	0.4	0.25	0.01	0.00	0.00	7.26
In Fig. 2.6 (second set of parameters)																	
0.72	2.0	0.5	0.5	0.5	0.01	0.8	0.01	0.4	0.2	0.2	0.1	0.4	0.25	0.01	0.75	0.25	0.32

In Fig. 2.6 we present four series of numerical experiments for which $R_0 = 7.26$ (first two lines) and $R_0 = 0.32$ (last two lines). It can be noted that the disease exists in populations (host and vector). Without vaccination or methods of reducing mosquito population, susceptible subpopulation is declining. At the same time, the representative curves of subpopulations (exposed, infected, and recovered) converge to equilibrium values, and we note a significant presence of the disease in the population. Vaccination was carried out in human population (second line of graph and first figure), which shows that the disease has practically disappeared, and the curves of other subpopulations converge to equilibrium values. The last two lines of the graph show that with vaccination and a method of preventing mosquito development, one can observe that the representative curves of the population (host and vector) quickly stabilize, and the disease disappears from the population.

Table 2.5: Parameters for the simulation, which results are presented in Fig. 2.7.

α	α_k	β	β_k	γ	μ	a	a'	a_k	a'_k	b	b_k	c	c_k	d	σ	dv	R_0
In Fig. 2.7 (first set of parameters)																	
0.8	2.5	0.4	0.6	0.45	0.02	0.4	0.25	0.5	0.25	0.15	0.2	0.25	0.3	0.05	0.00	0.00	10.36
In Fig. 2.7 (second set of parameters)																	
0.8	2.5	0.4	0.6	0.45	0.02	0.4	0.25	0.5	0.25	0.15	0.2	0.25	0.3	0.05	0.25	0.6	2.59

In Fig. 2.7 there are four series of simulations for which $R_0 = 10.36$ (first two lines of graphs) and $R_0 = 2.59$ (last two lines of graphs). It can be noted that the disease lasts in host and vector populations relatively long. At the same time, a representative curve of susceptible subpopulation decreases. At the same time, representative curves of the subpopulations (exposed, infected, and recovered) converge to equilibrium values, and a significant disease presence can be noted in the population. If control measures are not taken, there is a risk that the disease will remain in the population because the calculated basic reproduction number indicates that at least one infected person can infect several people. If human people has been vaccinated with a parameter of $dv = 0.6$ (second line of graph, first figure), then despite the fact that the disease still exists in the population, an infection rate de-

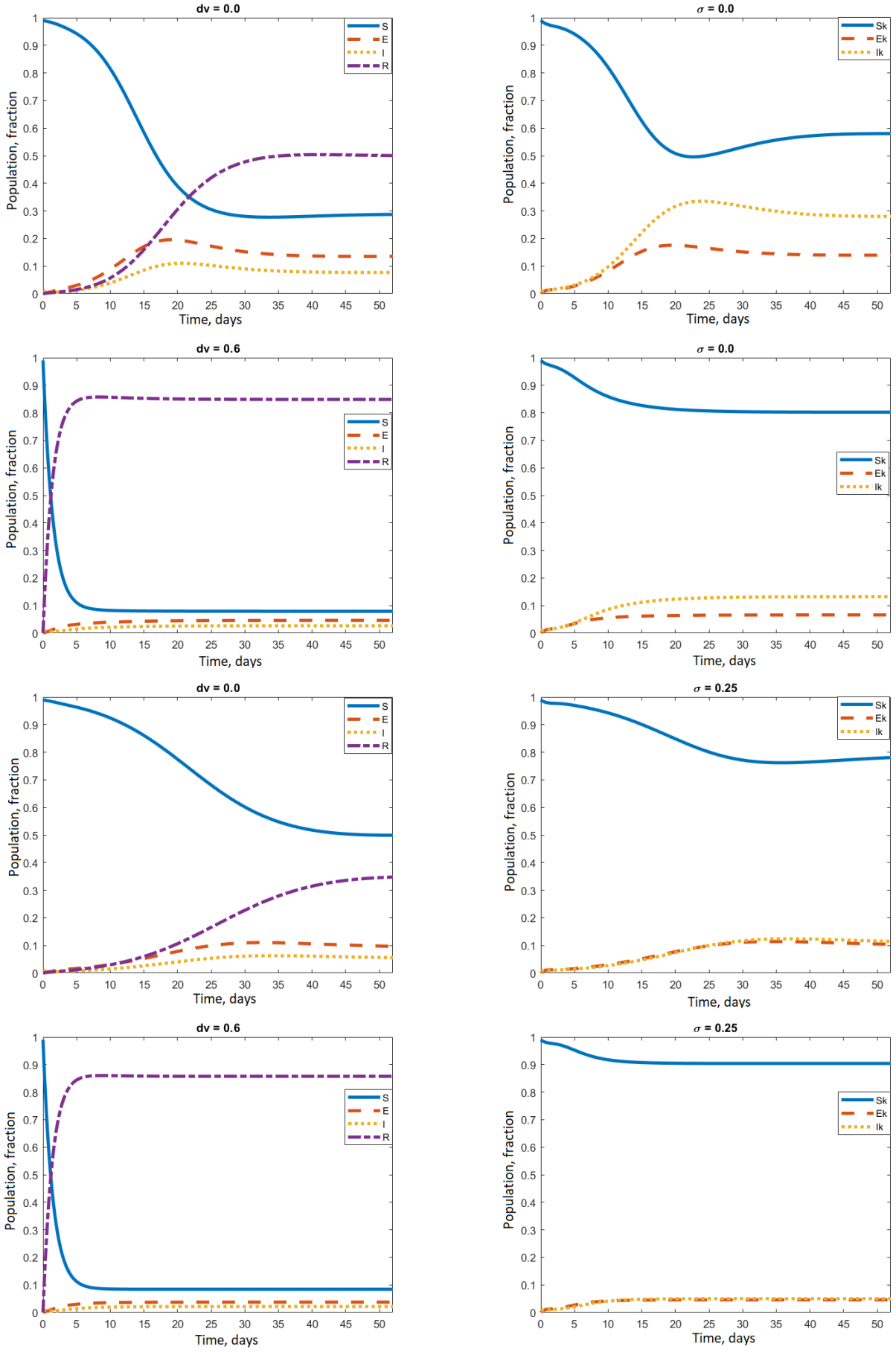

Figure 2.7: Epidemic process for different values of R_0 ($R_0 = 10.36$ and $R_0 = 2.59$).

creases due to vaccination of the population. The last two lines show that with the help of vaccination and a method of preventing mosquito development (parameter $\sigma = 0.25$), representative curves of populations (host and vector) gradually converge to equilibrium values.

In general, the results of numerical simulations show that a method of eliminating or preventing mosquito development is very effective in suppressing a rapid epidemic development, but it is very difficult and expensive for applying it in practice.

2.3 Conclusion to Chapter 2

Mathematical modeling of malaria plays a significant role in understanding the dynamics of transmitting infectious diseases and developing appropriate prevention methods. In this chapter, $SEIRS_kE_kI_k$ model is proposed for predicting malaria spread. At present, scientists have not succeeded in developing an effective vaccine against malaria. In this model, we explore two equilibrium points: disease-free equilibrium and endemic equilibrium. Using the theory of Lyapunov functions, the stability of two equilibrium points is studied. The simulation results have largely shown the disease spread among the population, and the effect of vaccination on disease spread.

Chapter 3

Two epidemiological models of malaria and their application on practice

This chapter uses the SIR model and the $CIRD$ model to predict annual dynamics of malaria epidemics from 2000 to 2027 based on annual data of malaria disease in Senegal [6]. A modified model SIR with constant coefficients is constructed, a description of the $CIRD$ balance model with stochastic parameters is given. The question about the accuracy of forecasting the annual statistical indicators of the epidemic when using these models is investigated. Numerical experiments show that an average error in forecasting the annual number of sick people in relation to actual statistical data when using the SIR model is quite large, while the $CIRD$ model gives more accurate forecasts in a comparative analysis.

3.1 Description of sample data

There is a sample of 22 observations of the annual malaria disease in Africa (using Senegal as an example) from 2020 to 2021. Each observation is a three-dimensional vector corresponding to a particular year, including the number of people in susceptible population, the number of infected people who have been tested, and the number of recovered people in each year. The available data are presented in the table (see Annex B). Based on the annual values of indicators, a new table is formed, in which the data are presented on an accrual basis.

3.2 Building modified SIR model based on statistical data

It is assumed that the entire human population is divided into several subpopulations. Any individual belongs to a single subpopulation. Despite the fact that the

SIR model is one of the simplest epidemic models, it is actively used in practice and contains some parameters that need to be estimated according to the available statistical data. Let the population consist of N people, which structure includes three nonoverlapping subgroups: susceptible S, infected I and recovered R.

The number of people in each of these subgroups is not constant and varies depending on the year. We will use the following notations:
$S(t)$ — size of susceptible subpopulation at time t;
$I(t)$ — size of infected subpopulation at time t;
$R(t)$ — size of recovered subpopulation (people with immunity) at time t;
α — increase rate of infected people;
β — increase rate of recovered people.

Let us write down a system of differential equations corresponding to the SIR model [2]:

$$\begin{cases} \dfrac{dS(t)}{dt} &= -\alpha\dfrac{S(t)I(t)}{N_0}, \\ \dfrac{dI(t)}{dt} &= \alpha\dfrac{S(t)I(t)}{N_0} - \beta I(t), \\ \dfrac{dR(t)}{dt} &= \beta I(t), \end{cases} \tag{3.1}$$

This system of differential equations is usually studied in the domain of admissible values: $\big\{(S, I, R) \in \mathbb{R}^3_+ : S + I + R = N\big\}$.

The proposed SIR system can be used to simulate a malaria epidemic under the initial conditions known at time $t = 0$ on any given time interval. The trajectories of the system, constructed taking into account the best selection of coefficients α and β, are usually time-deterministic functions, which, as shown by many examples in scientific literature, are often quite good approximations to the trajectories of changes in the population structure in real time. However, it is known that the length of the time interval with a slight approximation error is usually small. Assuming that the number of susceptible people at the beginning of the epidemics is proportional to a size of population N, i.e. $S \approx \gamma N$ and $\gamma \in [0, 1]$, we obtain a modified system of differential equations of type SIR:

$$\begin{cases} \dfrac{dS(t)}{dt} &= -\alpha\gamma I(t), \\ \dfrac{dI(t)}{dt} &= \alpha\gamma I(t) - \beta I(t), \\ \dfrac{dR(t)}{dt} &= \beta I(t), \end{cases} \tag{3.2}$$

The solution of a system of differential equations describing the dynamics of susceptible (S), infected (I) and recovered (R) populations is as follows:

$$\begin{aligned} I(t) &= I_0 e^{(\alpha\gamma-\beta)t}, \\ R(t) &= \tfrac{\beta I_0}{\alpha\gamma-\beta}(e^{(\alpha\gamma-\beta)t}-1)+R_0, \\ S(t) &= \tfrac{\alpha\gamma I_0}{(\alpha\gamma-\beta)}(1-e^{(\alpha\gamma-\beta)t})+\tfrac{\gamma}{1-\gamma}(I_0+R_0). \end{aligned} \tag{3.3}$$

Using the available initial data for variables of system (3.3), we construct predictive trajectories for the number of infected and recovered people using a modified SIR model (see Table 3.1 and Table 3.2).

As a rule, system (3.2) is used to describe epidemic dynamics on intervals which length does not significantly exceed disease duration. In our case of predicting annual values of the number of infected and recovered people, it is required that obtained trajectories of system (3.2) should be interpreted differently. Given the increasing nature of system solutions, we propose to compare the obtained predictive trajectories with integral actual data that summarize the corresponding values of actual annual indicators for all previous years. Thus, we entered exactly integral actual data into the second and third columns.

The values of parameters α, β, and γ were chosen from according to the condition of minimizing the approximation errors in constructed trajectories $\hat{I}(t)$ and $\hat{R}(t)$ using a modified model in comparison with the trajectories $I(t)$ and $R(t)$ actually realized in an interval from 2000 to 2021. The forecasting of these values is of the greatest interest to epidemiologists compared to forecasting of subpopulation S. As a result, for comparison the following parameter values are chosen: $\alpha = 0.4$, $\beta = 0.06$, $\gamma = 0.9$ (Table 3.1), and parameters $\alpha = 0.4$, $\beta = 0.1$, and $\gamma = 0.9$ (Table 3.2).

Fig. 3.1 and 3.2 are based on the data presented in Table 3.1, and Fig. 3.3 and 3.4 are built on data presented in Table 3.2, where blue represents actual malaria data defined from hospitals and orange represents predicted values obtained using the modified SIR model above.

An average approximation error is calculated by the formula:

$$M = \frac{1}{n}\sum_{i=1}^{n}\Big|\frac{A_i - F_i}{A_i}\Big|,$$

where A_i is an actual value and F_i is a predicted value.

3.2.1 Forecasting malaria epidemic in Senegal from 2000 to 2016

Table 3.1: Integrated actual malaria data for 2000-2016 and forecast based on modified SIR model

Year	$I(t)$	$R(t)$	$\hat{I}(t)$	$\hat{R}(t)$
2000	44959	44083	44959	44083
2001	57879	55861	44959	47229
2002	72304	69320	60688	51475
2003	99169	95138	81921	57207
2004	121403	116132	110581	64945
2005	154563	148030	149269	75390
2006	202633	194948	201492	89488
2007	320965	311845	271986	108520
2008	562891	553845	367143	134209
2009	728824	719853	495591	168887
2010	1059155	1050103	668978	215696
2011	1333274	1324303	903026	278883
2012	1613515	1604469	1218957	364175
2013	1980202	1971082	1645420	479308
2014	2249114	2241429	2221085	634721
2015	2741367	2734834	2998151	844507
2016	3090907	3085636	4047080	1127689

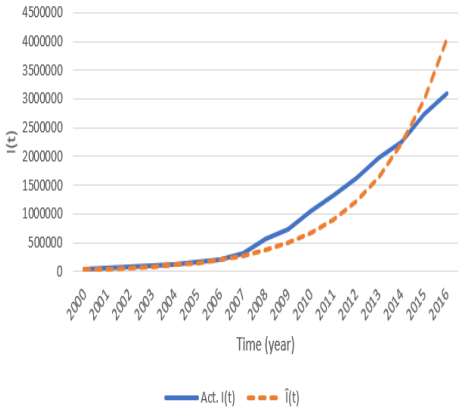

Figure 3.1: Integrated values of infected people $I(t)$ (actual data and predicted data obtained using modified SIR model)

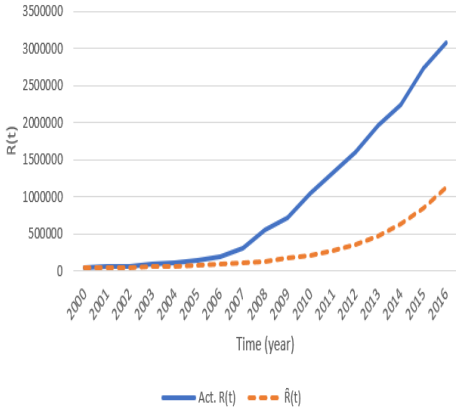

Figure 3.2: Integrated values of recovered $R(t)$ (actual data and predicted data obtained using modified SIR model)

The results of calculations of the SIR model are shown in Fig. 3.2 and Table 3.1. It can be seen that from 2000 to 2007 the model quite well reflects the dynamics

of the epidemic spread. The trajectories constructed for the best image coefficients of such a system are usually time-deterministic functions, which, as shown in many examples in scientific literature, are often quite good approximations of population change trajectories in real time. However, many factors influence the estimation accuracy, such as the quality of available statistics and the variability in the disease course. Unknown model parameters (α and β) can significantly reduce constructed forecast quality of the epidemiological situation dynamics. Coefficients α and β are generally random variables. The distribution functions of these random variables are not known in advance. The performance of a learning-based model is evaluated using the prediction error, also known as a mean approximation error. Measuring this performance is very important because, on the one hand, it allows to conduct model selection in the family associated with a learning method used, and, on the other hand, it guides method selection by comparing each of the optimized models with the previous step. Finally, in making any choice, it provides an indicator of quality, or even confidence, that can be given to the forecast. The choice depends on several factors, including a desired goal, a size of the original sample, the complexity of the model under consideration, error variance, and the complexity of algorithms. In constructed model from 2007 to 2016, there is a significant discrepancy between the calculated and actual data. An average approximation error of the calculated trajectory of the number of active cases for the period from 2000 to 2016 is 17.81%.

In Fig. 3.2 and Table 3.1, the results of calculations by a modified SIR model are presented. It can be seen that from 2000 to 2006 the model quite well reflects the dynamics of the epidemic spread. From 2006 to 2016, there is a growing discrepancy between the calculated and actual data. An average approximation error of the calculated trajectory of the integrated number of active cases (infected) for the period from 2000 to 2016 is 56.56%.

3.2.2 Forecasting the malaria epidemic in Senegal from 2000 to 2021

The results of calculations of the SIR model are shown in Fig. 3.3 and Table 3.2. It can be seen that from 2000 to 2007 the model quite well reflects the dynamics of the epidemic spread. From 2007 the 2021, there is a significant discrepancy between the calculated and actual data. An average approximation error of the calculated

Table 3.2: Actual malaria data for 2000-2021 and forecast based on modified SIR model

Year	$I(t)$	$R(t)$	$\hat{I}(t)$	$\hat{R}(t)$
2000	44959	44083	44959	44083
2001	57879	55861	44959	47229
2002	72304	69320	60688	51475
2003	99169	95138	81921	57207
2004	121403	116132	110581	64945
2005	154563	148030	149269	75390
2006	202633	194948	201492	89488
2007	320965	311845	271986	108520
2008	562891	553845	367143	134209
2009	728824	719853	495591	168887
2010	1059155	1050103	668978	215696
2011	1333274	1324303	903026	278883
2012	1613515	1604469	1218957	364175
2013	1980202	1971082	1645420	479308
2014	2249114	2241429	2221085	634721
2015	2741367	2734834	2998151	844507
2016	3090907	3085636	4047080	1127689
2017	3486613	3482582	5462987	1509943
2018	4017557	4014573	7374261	2025933
2019	4372265	4370247	9954211	2722447
2020	4817578	4816702	13436779	3662642
2021	5354428	5354428	18137755	4931773

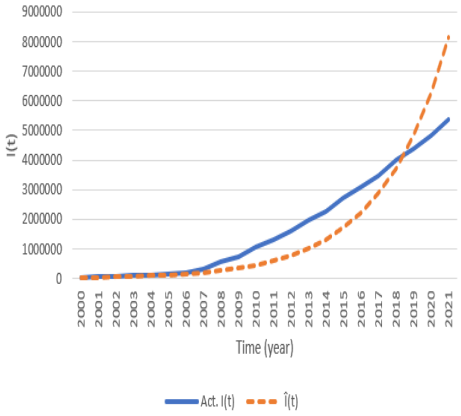

Figure 3.3: Integrated values of infected people $I(t)$ (actual data and data predicted using modified SIR model)

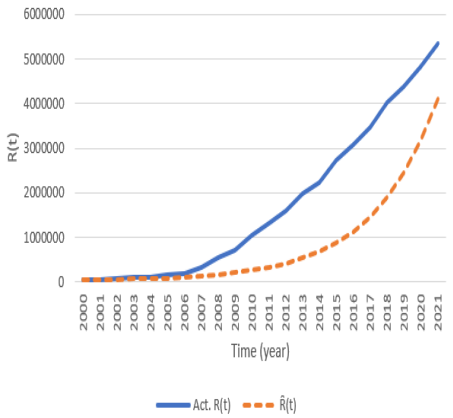

Figure 3.4: Integrated values of recovered people $R(t)$ (actual data and data predicted using modified SIR model)

trajectory of the number of active cases from 2000 to 2021 is 31.40%.

In Fig. 3.4 and Table 3.2, the results of calculations by a modified SIR model

are presented. It can be seen that from 2000 to 2006 the model quite well reflects the dynamics of the epidemic spread. From 2006 to 2021, there is a significant discrepancy between the calculated and actual data. An average approximation error of the calculated trajectory of the number of active cases from 2000 to 2021 is 49.58%.

3.3 Balance model of malaria

3.3.1 Description of balance model of malaria epidemic based on percentage increase

Consider balance malaria model, built on the basis of the CIR model presented in [1]. Denote the total number of reported malaria cases by $C(t)$ for $t = 0, 1, 2, \ldots$ The number of new cases $\Delta(t)$ at time t can be calculated by the formula

$$\Delta(t) = C(t) - C(t-1).$$

The percentage increase $r(t)$ of $C(t)$ at time t is denoted by $r(t)$ and written as

$$r(t) = 100\frac{\Delta(t)}{C(t-1)}.$$

The discrete equation for variable $C(t)$ can then be written as

$$C(t) = \Big(1 + \frac{r(t)}{100}\Big)C(t-1).$$

Denote by $R(t)$ the total number of recovered or died patients by time t. Assuming that disease duration is generally a finite value, for any given time $T > 0$, consider the inequalities:

$$C(t) \geq R(T), \;\; 0 < t \leq T.$$

Taking into account nondecreasing nature of function $C(t)$ relative to variable t and limited interval $0 \leq t \leq T$, integer programming problem

$$\min_{0<t\leq T} t,$$
$$C(t) \geq R(T)$$

has a solution, which we denote by $\tau(T)$.

Then, in accordance with the principle of dynamic balance of the epidemiological process [21], for any time t, $0 < t \leq T$ the following inequality is true:

$$C(\tau(t)) \geq R(t) \geq C(\tau(t) - 1).$$

In this case, value $R(t)$ will belong to interval $[C(\tau(t)-1), C(\tau(t))]$ and can be represented as

$$R(t) = \lambda_t C(\tau(t)-1) + (1-\lambda_t)C(\tau(t)), \;\; 0 \le \lambda_t \le 1.$$

The dynamics of the number of infected people (active cases) $I(t)$, taking into account balance ratio $C(t) = I(t) + R(t)$, can be set as follows:

$$I(t) = \Big(1 + \frac{r(t)}{100}\Big)C(t-1) - R(t).$$

Thus, the system of discrete equations describing malaria epidemic spread in host population will have the form:

$$\begin{aligned} C(t) &= \Big(1 + \frac{r(t)}{100}\Big)C(t-1), \\ I(t) &= \Big(1 + \frac{r(t)}{100}\Big)C(t-1) - R(t), \\ R(t) &= \lambda_t C(\tau(t)-1) + (1-\lambda_t)C(\tau(t)). \end{aligned}$$

Quantity $\theta(t) = t - \tau(t)$ is called the characteristic of dynamic balance of an epidemiological process [1]. A percentage increase and the characteristic of dynamic balance, as a rule, are nonstationary random variables. To predict the values of percentage increase $r(t)$, you can use a scenario approach or CBRR approach [1]. Forecasting the values of dynamic balance characteristic on prediction interval $[t, t+\theta(t)]$ can be carried out under the assumption of stationarity or nonstationarity of dynamic balance characteristic on this interval.

Let $\sigma(t)$ be a proportion of people who died during epidemic $D(t)$ out of total number $R(t)$. The value of $\sigma(t)$ is a coefficient (indicator) of the current lethality of an epidemiological process. Then the total number of dead people by time t can be written as the equation:

$$D(t) = \sigma(t)R(t).$$

Taking into account representation of $R(t)$ in the above equation, we obtain the following expression:

$$D(t) = \sigma(t)(\lambda_t C(\tau(t)-1) + (1-\lambda_t)C(\tau(t))).$$

Let us write a new system of discrete equations, which we will call the $CIRD$

model:

$$
\begin{aligned}
C(t) &= \Big(1 + \frac{r(t)}{100}\Big) C(t-1), \\
I(t) &= \Big(1 + \frac{r(t)}{100}\Big) C(t-1) - R(t), \\
R(t) &= \lambda_t C(\tau(t) - 1) + (1 - \lambda_t) C(\tau(t)), \\
D(t) &= \sigma(t)(\lambda_t C(\tau(t) - 1) + (1 - \lambda_t) C(\tau(t))).
\end{aligned}
$$

3.3.2 Practical application of stochastic balance model

In this section, we will study stochastic predictions of malaria. The study is based on the article [20], which examines a balance model of the epidemic of new viruses based on a percentage increase and characteristic of dynamic balance, which have stochastic nature. A high accuracy of forecasting future dynamics of main statistical indicators of the *COVID-19* pandemic in Russia has been confirmed by many numerical experiments. The database used represents an annual malaria evolution in Senegal (Africa) from 2000 to 2021.

The data in the tables below are structured as follows: column 2 contains actual data on the total number of reported cases $C(t)$ since 2020, column 3 contains integrated actual data on infected population $I(t)$, column 4 contains integrated actual data on recovered population $R(t)$, column 5 contains data on deceased population $D(t)$, column 6 contains values of dynamic balance characteristic $\theta(t)$, column 7 contains predicted data for total number of reported cases $\hat{C}(t)$, column 8 contains predicted data for infected population $\hat{I}(t)$, column 9 contains predicted data for recovered population $\hat{R}(t)$, and the 10 column contains predicted data on deceased population $\hat{D}(t)$.

3.3.3 Model forecast for 2011-2017

Table 3.3: Actual malaria data for 2011-2017 and forecast based on modified $CIRD$ model

Year	$C(t)$	$I(t)$	$R(t)$	$D(t)$	$\theta(t)$	$\hat{C}(t)$	$\hat{I}(t)$	$\hat{R}(t)$	$\hat{D}(t)$
2000	89042	44959	44083	399					
2001	113740	57879	55861	772	1				
2002	141624	72304	69320	1032	2				
2003	194307	99169	95138	1587	2				
2004	237535	121403	116132	1871	2				
2005	302593	154563	148030	2196	2				
2006	397581	202633	194948	2722	2				
2007	632810	320965	311845	3222	1				
2008	1116736	562891	553845	4037	1				
2009	1448677	728824	719853	4686	1				
2010	2109258	1059155	1050103	5158	2				
2011	2657577	1333274	1324303	5711	2	2636484	1353778	1282707	5516
2012	3217984	1613515	1604469	6285	2	3191408	1908702	1282707	7650
2013	3951284	1980202	1971082	7026	3	3816514	2037546	1778968	10249
2014	4490543	2249114	2241429	8961	3	4544977	2161560	2383418	12632
2015	5476201	2741367	2734834	10639	3	5389759	2451978	2937781	15414
2016	6176543	3090907	3085636	12226	4	6364612	2779978	3584634	18150
2017	6969195	3486613	3482582	13750	4	7483965	3263051	4220914	21429

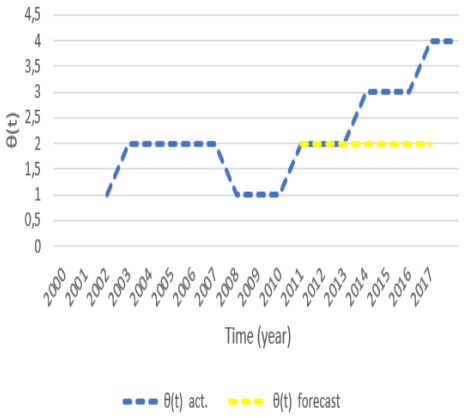

Figure 3.5: Actual values of dynamic balance characteristic for 2000-2017 and predicted (stationary) values for 2011-2017

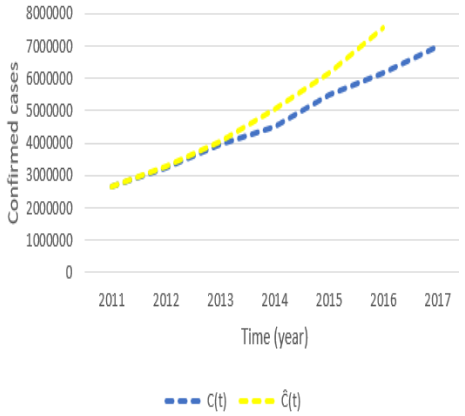

Figure 3.6: Actual and predicted dynamics of total number of cases for 2011-2017

Based on the data available from 2000 to 2021, we will build a forecast for disease course for 2011-2017. The forecasting is carried out using intelligent algorithms for constructing piecewise linear trends of stochastic values of a percentage increase and the characteristic of dynamic balance (under the assumption of its stationarity or nonstationarity). The graphs of actual and predicted values of the dynamic balance

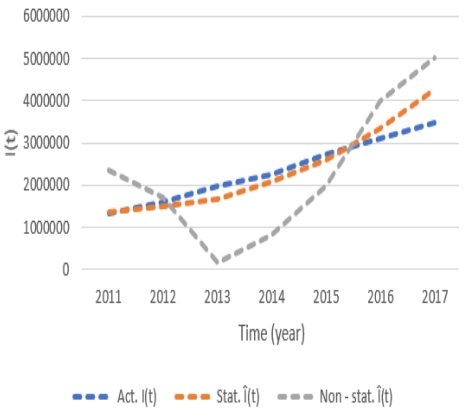

Figure 3.7: Dynamics of actual and simulated trajectories $I(t)$ from 2011 to 2017, in stationary and nonstationary cases of dynamic balance characteristic

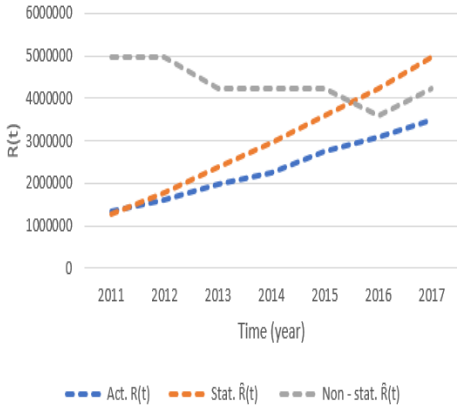

Figure 3.8: Dynamics of actual and simulated trajectories $R(t)$ from 2011 to 2017, in stationary and nonstationary cases of dynamic balance characteristic

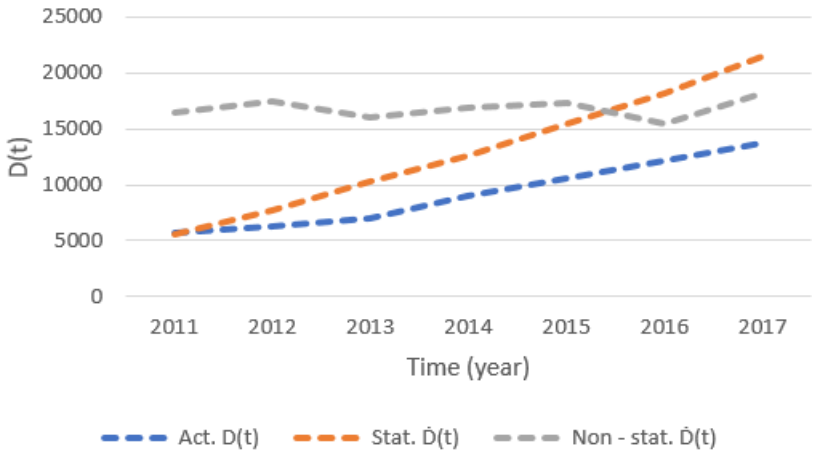

Figure 3.9: Dynamics of actual and calculated trajectories $D(t)$ for years from 2011 to 2017 in stationary case and in case of updated values of $D(t)$

characteristic in a stationary case are shown in Fig. 3.5. The graphs of actual and predicted trajectories of model variables are shown in Fig. 3.6-3.9.

From 2011 to 2017, value $\theta = 2$ is used in forecasts. The plot of estimated data for infected population almost perfectly reflects actual data for infected population. An average approximation error is 9.44%. Similarly, the plots of actual and estimated deaths have an average approximation error of 37.31%.

3.3.4 Model forecast for 2018-2021

From 2018 to 2021, the forecasts use value $\theta = 4$ and an assumption of a slight decrease $r(t)$. The evolution of dynamic balance characteristic, as well as actual and

Table 3.4: Actual malaria data for 2018-2021 and prediction using $CIRD$ model and stationary conditions

Year	$C(t)$	$I(t)$	$R(t)$	$D(t)$	$\theta(t)$	$\hat{C}(t)$	$\hat{I}(t)$	$\hat{R}(t)$	$\hat{D}(t)$
2000	89042	44959	44083	399					
2001	113740	57879	55861	772	1				
2002	141624	72304	69320	1032	2				
2003	194307	99169	95138	1587	2				
2004	237535	121403	116132	1871	2				
2005	302593	154563	148030	2196	2				
2006	397581	202633	194948	2722	2				
2007	632810	320965	311845	3222	1				
2008	1116736	562891	553845	4037	1				
2009	1448677	728824	719853	4686	1				
2010	2109258	1059155	1050103	5158	2				
2011	2657577	1333274	1324303	5711	2				
2012	3217984	1613515	1604469	6285	2				
2013	3951284	1980202	1971082	7026	3				
2014	4490543	2249114	2241429	8961	3				
2015	5476201	2741367	2734834	10639	3				
2016	6176543	3090907	3085636	12226	4				
2017	6969195	3486613	3482582	13750	4				
2018	8032130	4017557	4014573	15352	4	7793878	3572965	4220914	16039
2019	8742512	4372265	4370247	16578	5	8677179	3693807	4983372	18937
2020	9634280	4817578	4816702	18093	5	9617200	3790828	5826372	22140
2021	10708856	5354428	5354428	19368	6	10610971	4038102	6572869	24976

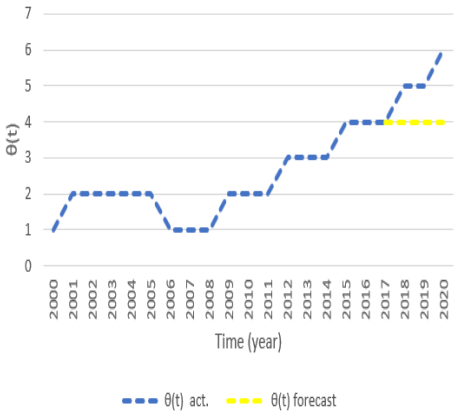

Figure 3.10: Actual and simulated values of dynamic balance characteristic $\theta(t)$ for 2000-2020

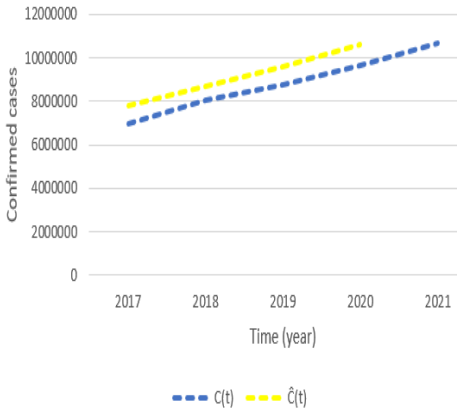

Figure 3.11: Dynamics of actual and simulated trajectories $C(t)$ for 2017-2021

forecast trajectories of main variables are graphically presented in Fig. 3.11-3.14. The plot of estimated data for infected population almost perfectly reflects actual data for infected population. An average approximation error is 18.12%. Similarly, the plots of actual and estimated deaths have an average approximation error of 17.51%.

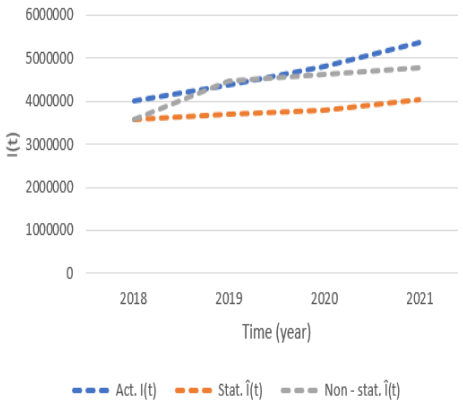

Figure 3.12: Dynamics of actual and simulated trajectories $I(t)$ for 2018-2021, in stationary and nonstationary cases of dynamic balance characteristic

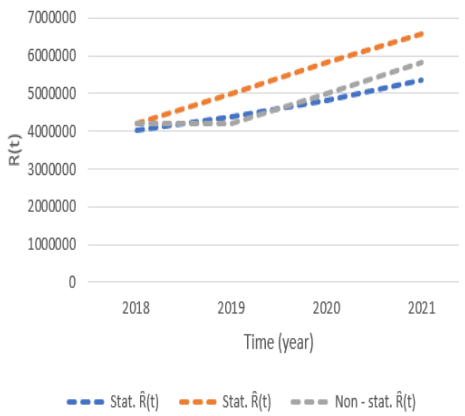

Figure 3.13: Dynamics of actual and simulated trajectories $R(t)$ for 2018-2021, in stationary and nonstationary cases of dynamic balance characteristic

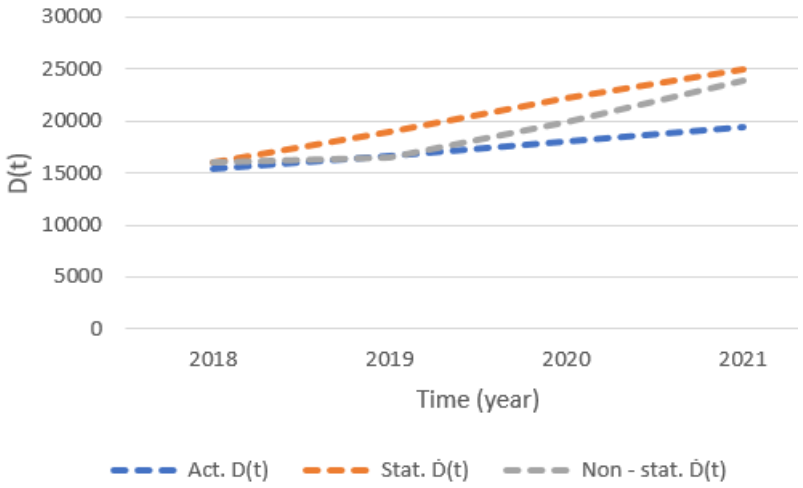

Figure 3.14: Dynamics of actual and calculated trajectories $D(t)$ for 2018-2021 in stationary case and in case of updated values of $D(t)$

Model forecast for 2021-2027

This section presents the malaria forecast for the next 5 years. Data for forecasting are given in the Table 3.5.

Simulations are performed along with the intervals used to predict malaria situation over the next 5 years (i.e. from 2022 to 2027). The values obtained in forecasts are given in Table 3.5. The plots of data modeling for the number of recovered cases $\hat{R}(t)$, active cases $\hat{I}(t)$, and the number of deaths $D(t)$ are shown in Fig. 3.15, 3.16 and 3.17. Nonstationary data are also presented on the graphs.

Table 3.5: Actual malaria data and forecast for 2021-2027 based on modified $CIRD$ model

Year	$C(t)$	$I(t)$	$R(t)$	$D(t)$	$\theta(t)$	$\hat{C}(t)$	$\hat{I}(t)$	$\hat{R}(t)$	$\hat{D}(t)$
2000	89042	44959	44083	399					
2001	113740	57879	55861	772	1				
2002	141624	72304	69320	1032	2				
2003	194307	99169	95138	1587	2				
2004	237535	121403	116132	1871	2				
2005	302593	154563	148030	2196	2				
2006	397581	202633	194948	2722	2				
2007	632810	320965	311845	3222	1				
2008	1116736	562891	553845	4037	1				
2009	1448677	728824	719853	4686	1				
2010	2109258	1059155	1050103	5158	2				
2011	2657577	1333274	1324303	5711	2				
2012	3217984	1613515	1604469	6285	2				
2013	3951284	1980202	1971082	7026	3				
2014	4490543	2249114	2241429	8961	3				
2015	5476201	2741367	2734834	10639	3				
2016	6176543	3090907	3085636	12226	4				
2017	6969195	3486613	3482582	13750	4				
2018	8032130	4017557	4014573	15352	4				
2019	8742512	4372265	4370247	16578	5				
2020	9634280	4817578	4816702	18093	5				
2021	10708856	5354428	5354428	19368	6	10708856	4983372	5725484	17940
2022						11671792	5826372	5845420	20975
2023						12552357	6572869	5979488	23662
2024						13317652	7500663	5816989	27002
2025						13936823	8387321	5549502	30194
2026						14383036	9188396	5194640	33078
2027						14635331	10171568	4463763	36618

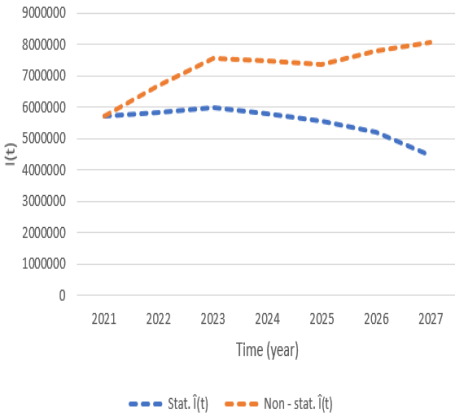

Figure 3.15: Dynamics of simulated trajectories $I(t)$ for 2021-2027, in stationary case and with updated values of $I(t)$

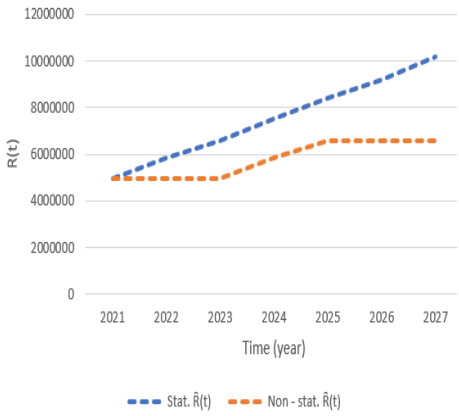

Figure 3.16: Dynamics of simulated trajectories $R(t)$ for 2021-2027, in stationary case and with updated values of $R(t)$

The results obtained in the field of disease forecasting show that the number of recovered people increases significantly, while the number of infected people decreases. It can be noted that the disease can disappear if preventive measures to combat the

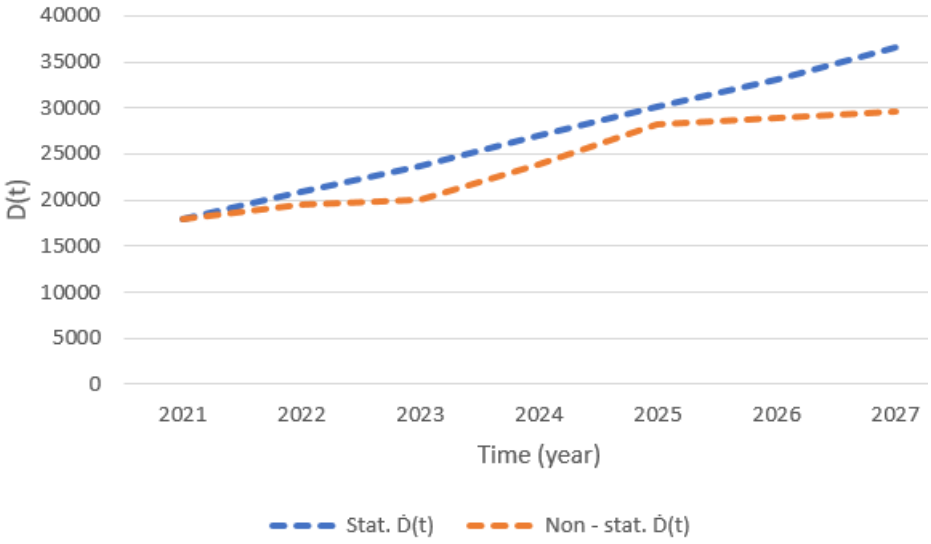

Figure 3.17: Dynamics of $D(t)$, actual and calculated trajectories in the interval from 2021 to 2027 in the stationary case and in the case of updated values of $D(t)$

disease are taken.

3.4 Conclusion to Chapter 3

Chapter 3 presents two models of a malaria epidemic process and their application in practice. The first model is based on the classical SIR model and modified to describe the development of malaria in Senegal in the form of annual data. The main feature of the modified SIR model, in contrast to a classical version, is that it is suitable for modeling on intervals which length (one year) significantly exceeds disease duration. Predicted values are compared with the actual data presented in an integrated form, for various time intervals, the average approximation errors are obtained, on the basis of which a conclusion is made about the possibility of using the model to predict the number of active cases and the total number of recovered people. The second model is based on the principle of dynamic balance of an epidemiological process and takes into account when making forecasts generated dynamic trends of stochastic values of a percentage increase in the total number of cases and assumptions about stationary or nonstationary nature of a change in the dynamic balance characteristic. The estimators obtained for selected forecast intervals demonstrate a higher accuracy of the balance model forecasts for estimating future values of active cases and a size of a recovered part of the population.

Chapter 4

Coalitional Differential Game of Vaccine Manufacturers

The chapter proposes a game-theoretic model of competition and cooperation, including partial cooperation, of vaccine manufacturers. Various versions of players' cooperation (partial and full) have been studied. The differential game has infinite duration. For each possible coalition of players, the profits and production of its members are determined. A stability analysis of possible coalition structures, as well as the most attractive coalitions for buyers, has been carried out [9].

4.1 Model

We consider a model of a market consisting of firms manufacturing vaccine (or other production firms) that produce vaccines to fight the same disease, i.e. their vaccines can substitute each other. Denote by $N = \{1, 2, \dots, n\}$ a set of firms, each of which has production of $q_i(\cdot)$: $[0, +\infty) \longrightarrow \mathbb{R}^+$ [33]. The total production Q_i of firm i over the entire time interval $[0, +\infty)$ is equal to

$$Q_i = \int_0^{+\infty} q_i(t)\,\mathrm{d}t.$$

Suppose that the initial vaccine price is given as $p(0) = p_0$, and at any time t the price satisfies a differential equation:

$$\dot{p}(t) = s\Big(a - b\sum_{i=1}^{n} q_i(t) - p(t)\Big),\ p(0) = p_0, \tag{4.1}$$

where a and b are positive constants, while $a > c$ and $a - bQ \geq 0$, $s > 0$ is the parameter of price sensitivity to changes. Price dynamics (4.1) takes into account that a market price does not adapt immediately to market changes. A rate of

change in a market price is determined by the difference between the current price and the price formed by a linear demand function, multiplied by the given constant s. Constant s shows market sensitivity to price changes. Firms are also assumed to have a quadratic function of production costs:

$$C(q_i) = c_i q_i + \frac{1}{2} {q_i}^2,$$

where c_i is a positive constant for any $i \in N$.

The profit of firm i is determined by the functional

$$J_i(q_1, \ldots, q_n) = \int_0^{+\infty} e^{-rt} \left(p(t) q_i(t) - c_i q_i(t) - \frac{1}{2} q_i^2(t) \right) \, \mathrm{d}t, \tag{4.2}$$

where $r > 0$ is a discount rate, the same for all players.

The differential game is defined by a set of players N, the players' payoff functions (4.2), and dynamics equation (4.1), while player $i \in N$ maximizes function (4.2) by choosing strategies $q_i(t)$. Denote the total output by $Q(t) = \sum_{i=1}^{n} q_i(t)$ [33].

As a solution, we will consider the Nash equilibrium in program strategies (open-loop strategies).

Definition 4.1. *Nash equilibrium is a set of strategies* $q^* = (q_1^*, q_2^*, \ldots, q_n^*)$ *such that*

$$J_i(q_i^*, q_{-i}^*) \geq J_i(q_i, q_{-i}^*),$$

for any $q_i \geq 0$ *and for any player* $i \in N$.

In the next section, we consider a modification of a noncooperative differential game, assuming that players can cooperate, i.e. form coalitions of any sizes, thereby creating coalition partitions or structures of a set of players N. We make several assumptions about players' behavior in coalition structures:

1. If coalition structure $\pi = \{B_1, \ldots, B_m\}$ is formed, consisting of m nonempty subsets of a set of players such that $B_i \cap B_j = \varnothing$ for any $i \neq j$, and $\cup_{k=1}^{m} B_k = N$, then players belonging to the same coalition maximize the total profit of this coalition.

2. Coalitions $B_1, \ldots, B_m$ compete in the market, i.e. in the noncooperative setting, the optimality principle is the Nash equilibrium in a game of m players.

3. Players' payoffs are nontransferable, i.e. any player in a coalition receives its payoff according to the payoff function given by formula (4.2).

4.2 Case of Three-Person Game with Different Coalition Structures

In this section, we formulate the necessary conditions of the Nash equilibria for the differential game described in the previous section and given coalition structures. The results are shown for a case of a three-person game, but if desired, they can be generalized to the case of a finite number of players. With a large number of players, the number of coalition structures determined by the Bell number in a recurrent way, is so large that it is not possible to provide conditions for the Nash equilibrium in a general case. For example, for five players the number of coalition structures is 52, for seven players it is equal to 877, and for ten players it equals 115975.

4.2.1 Noncooperative game

Theorem 4.1. *In a three-person differential game defined by the players' payoff functions* (4.2)*, dynamics equation* (4.1)*, and coalition structure* $\{\{i\},\{j\},\{k\}\}$*, if the Nash equilibrium in admissible open-loop strategies exists, then it satisfies the system:*

$$
\begin{aligned}
q_i(t) = \frac{w_1 + w_3 + 3sbB_1B_2}{w_1 + w_3}\Big(&\frac{p_0(b(3r+4s)+r+s)}{b(3r+4s)+r+s} \\
&- \frac{((c_i+c_j+c_k+a)s + r(c_i+c_j+c_k))b}{b(3r+4s)+r+s} \\
&+ \frac{a(r+s)}{b(3r+4s)+r+s}\Big)e^{-w_1 t} + \frac{sbB_2B_3}{w_3} \\
&+ \frac{((c_i+c_j+c_k+a)s + r(c_i+c_j+c_k))b + a(r+s)}{b(3r+4s)+r+s} - c_i,
\end{aligned}
$$

$$
\begin{aligned}
q_j(t) = \frac{w_1+w_3+3sbB_1B_2}{w_1+w_3}\Big(&\frac{p_0(b(3r+4s)+r+s)}{b(3r+4s)+r+s}\\
&-\frac{((c_i+c_j+c_k+a)s+r(c_i+c_j+c_k))b}{b(3r+4s)+r+s}\\
&+\frac{a(r+s)}{b(3r+4s)+r+s}\Big)e^{-w_1t}+\frac{sbB_2B_4}{w_3}\\
&+\frac{((c_i+c_j+c_k+a)s+r(c_i+c_j+c_k))b+a(r+s)}{b(3r+4s)+r+s}-c_j,\\
q_k(t) = \frac{w_1+w_3+3sbB_1B_2}{w_1+w_3}\Big(&\frac{p_0(b(3r+4s)+r+s)}{b(3r+4s)+r+s}\\
&-\frac{((c_i+c_j+c_k+a)s+r(c_i+c_j+c_k))b}{b(3r+4s)+r+s}+\\
&+\frac{a(r+s)}{b(3r+4s)+r+s}\Big)e^{-w_1t}+\frac{sbB_2(B_3-B_4)}{w_3}\\
&+\frac{((c_i+c_j+c_k+a)s+r(c_i+c_j+c_k))b+a(r+s)}{b(3r+4s)+r+s}+\\
&-sb\frac{c_i+c_j+c_k-3a}{b(3r+4s)+r+s}-c_k,
\end{aligned}
$$

where

$$
\begin{aligned}
w_1 &= \frac{-2sb+r-\sqrt{\Delta}}{2},\\
\Delta &= (4b^2+16b+4)s^2+(8rb+4s)s+r^2,\\
w_3 &= bs+s+r,\\
B_1 &= b(r+\frac{4}{3}s)+\frac{r+s}{3},\\
B_2 &= -\frac{1}{b(3r+4s)+r+s},\\
B_3 &= ((-3c_i+c_j+c_k+a)s-r(2c_i-c_j-c_k))b+(r+s)(a-c_i),\\
B_4 &= ((c_i-3c_j+c_k+a)s-r(c_i-2c_j+c_k))b+(r+s)(a-c_j).
\end{aligned}
$$

The expression of the Nash equilibrium price is given in the theorem proof.

Proof. Under coalition structure $\{\{i\},\{j\},\{k\}\}$, each firm individually maximizes its profit by choosing production. To find the Nash equilibrium in open-loop strategies, we use the Pontryagin maximum principle. The Hamiltonian of player $i \in N$ has the form:

$$
H_i(q,p,\lambda_i) = pq_i - c_iq_i - \frac{1}{2}{q_i}^2 + s(a-bQ-p)\lambda_i, \tag{4.3}
$$

where λ_i is an adjoint variable.

Maximizing Hamiltonian H_i by production q_i, we obtain the equation:

$$p - c_i - q_i - sb\lambda_i = 0,$$

from where we express q_i:

$$q_i = p - sb\lambda_i - c_i. \tag{4.4}$$

The system of differential equations with respect to λ_i, $i \in N$, and p is written as follows:

$$\dot{\lambda}_i = r\lambda_i - \frac{\partial H_i}{\partial p} = -p + (r + s + sb)\lambda_i + c_i,\ i \in N,$$
$$\dot{p} = -(snb + s)p + s^2b^2 \sum_{i \in N} \lambda_i + sb \sum_{i \in N} c_i + sa.$$

We write down the system of $n + 1 = 4$ differential equations:

$$\begin{cases} \dot{p} &= -(3sb + s)p + s^2b^2(\lambda_i + \lambda_j + \lambda_k) + sb(c_i + c_j + c_k) + sa, \\ \dot{\lambda}_i &= -p + (sb + r + s)\lambda_i + c_i, \\ \dot{\lambda}_j &= -p + (sb + r + s)\lambda_j + c_j, \\ \dot{\lambda}_k &= -p + (sb + r + s)\lambda_k + c_k. \end{cases}$$

Then rewrite this system of differential equations in a matrix form:

$$\begin{pmatrix} \dot{p} \\ \dot{\lambda}_i \\ \dot{\lambda}_j \\ \dot{\lambda}_k \end{pmatrix} = \begin{pmatrix} -3sb - s & s^2b^2 & s^2b^2 & s^2b^2 \\ -1 & r + s + sb & 0 & 0 \\ -1 & 0 & r + s + sb & 0 \\ -1 & 0 & 0 & r + s + sb \end{pmatrix} \begin{pmatrix} p \\ \lambda_i \\ \lambda_j \\ \lambda_k \end{pmatrix} + \\ + \begin{pmatrix} sa + sb(c_i + c_j + c_k) \\ c_i \\ c_j \\ c_k \end{pmatrix}.$$

We find a solution to this system, i.e., λ_i, λ_j, λ_k and p, and to do this, we write a characteristic equation corresponding to the matrix of the system of differential equations. Characteristic equation

$$\begin{vmatrix} -3sb - s - w & s^2b^2 & s^2b^2 & s^2b^2 \\ -1 & r + s + sb - w & 0 & 0 \\ -1 & 0 & r + s + sb - w & 0 \\ -1 & 0 & 0 & r + s + sb - w \end{vmatrix} = 0$$

has three roots w_1, w_2 and w_3, which are written as

$$w_{1,2} = \frac{-2sb + r \pm \sqrt{\Delta}}{2},$$
$$w_3 = bs + s + r,$$

where

$$\Delta = (4b^2 + 16b + 4)s^2 + (8rb + 4s)s + r^2.$$

Solutions λ_i, λ_j, λ_k and p can be written as follows:

$$\lambda_i(t) = -\frac{3B_1B_2}{w_1 + w_3}A_3e^{-w_1t} - \frac{3B_1B_2}{w_3 - w_2}A_4e^{w_2t} + A_2e^{w_3t} - \frac{B_2B_3}{w_3},$$
$$\lambda_j(t) = -\frac{3B_1B_2}{w_1 + w_3}A_3e^{-w_1t} - \frac{3B_1B_2}{w_3 - w_2}A_4e^{w_2t} + A_1e^{w_3t} - \frac{B_2B_4}{w_3},$$

$$\begin{aligned}
\lambda_k(t) &= B_5B_6(\lambda_i + \lambda_j - A_1e^{w_3t} + A_2e^{w_3t}) \\
&\quad + B_5(B_7 + (B_8 + 4bB_9 + B_9)s \\
&\quad - (3b + 1)r^2 + (3bB_9 - B_9)r)A_3e^{-w_1t} \\
&\quad + B_5(B_7 + (B_8 - 4bB_9 - B_9)s - (3b + 1)r^2 \\
&\quad - (3bB_9 + B_9)r)A_4e^{w_2t} - \frac{c_i + c_j + c_k - 3a}{(s(4b + 1) + r(3b + 1))}, \\
p(t) &= A_4e^{w_2t} + A_3e^{-w_1t} \\
&\quad + \frac{((c_i + c_j + c_k + a)s + r(c_i + c_j + c_k))b + a(r + s)}{b(3r + 4s) + r + s},
\end{aligned}$$

where

$$\begin{aligned}
B_1 &= b(r + \frac{4}{3}s) + \frac{r + s}{3}, \\
B_2 &= -\frac{1}{b(3r + 4s) + r + s}, \\
B_3 &= ((-3c_i + c_j + c_k + a)s - r(2c_i - c_j - c_k))b + (r + s)(a - c_i), \\
B_4 &= ((c_i - 3c_j + c_k + a)s - r(c_i - 2c_j + c_k))b + (r + s)(a - c_j), \\
B_5 &= -\frac{1}{2s^2b^2(s(4b + 1) + r(3b + 1))}, \\
B_6 &= s^3(8b^3 + 2b^2) + rs^2(6b^3 + 2b^2), \\
B_7 &= -s^2(16b^2 + 12b + 2), \\
B_8 &= -r(12b^2 + 14b + 3), \\
B_9 &= \sqrt{4s^2b^2 + 8brs + 16bs^2 + r^2 + 4rs + 4s^2},
\end{aligned}$$

and A_1, A_2, A_3, and A_4 are constants determined from the initial and limit conditions: $p(0) = p_0$ and $\lim_{t\to\infty} e^{-rt}\lambda_i(t) = 0$, $\lim_{t\to\infty} e^{-rt}\lambda_j(t) = 0$, and $\lim_{t\to\infty} e^{-rt}\lambda_k(t) = 0$.

From condition $\lim_{t\to\infty} e^{-rt}\lambda_i(t) = 0$ it follows that $A_2 = 0$ and $A_4 = 0$, and from condition $\lim_{t\ to\infty} e^{-rt}\lambda_j(t) = 0$ it follows that $A_1 = 0$ and $A_4 = 0$, then

$$\lambda_i(t) = -\frac{3B_1B_2}{w_1+w_3}A_3e^{-w_1t} - \frac{B_2B_3}{w_3},$$

$$\lambda_j(t) = -\frac{3B_1B_2}{w_1+w_3}A_3e^{-w_1t} - \frac{B_2B_4}{w_3},$$
$$\lambda_k(t) = B_{10}A_3e^{-w_1t} - \frac{B_2B_5B_6(B_3+B_4)}{w_3} - \frac{c_i+c_j+c_k-3a}{(s(4b+1)+r(3b+1))},$$

where

$$B_{10} = -\frac{6B_1B_2B_5B_6}{w_1+w_3} + B_5B_7 + B_5B_8s + B_5B_9s(4b+1) - B_5r^2(3b+1) + B_5B_9r(3b+1),$$

then p can be written as:

$$p(t) = A_3e^{-w_1t} + \frac{((c_i+c_j+c_k+a)s + r(c_i+c_j+c_k))b + a(r+s)}{b(3r+4s)+r+s}.$$

Given the initial condition $p(0) = p_0$, we find the constant

$$A_3 = \frac{p_0(b(3r+4s)+r+s) - ((c_i+c_j+c_k+a)s + r(c_i+c_j+c_k))b}{b(3r+4s)+r+s} + \frac{+a(r+s)}{b(3r+4s)+r+s}.$$

Thus, after transformations, we get:

$$p(t) = -\frac{((c_i+c_j+c_k+a)s + r(c_i+c_j+c_k))b}{b(3r+4s)+r+s}e^{-w_1t} + \frac{p_0(b(3r+4s)+r+s) + a(r+s)}{b(3r+4s)+r+s}e^{-w_1t} + \frac{((c_i+c_j+c_k+a)s + r(c_i+c_j+c_k))b + a(r+s)}{b(3r+4s)+r+s},$$

$$\lambda_i(t) = -\frac{3B_1B_2}{w_1+w_3}\frac{p_0(b(3r+4s)+r+s)}{b(3r+4s)+r+s}e^{-w_1t} + \frac{3B_1B_2}{w_1+w_3}\frac{((c_i+c_j+c_k+a)s + r(c_i+c_j+c_k))b}{b(3r+4s)+r+s}e^{-w_1t} + \frac{a(r+s)}{b(3r+4s)+r+s}e^{-w_1t} - \frac{B_2B_3}{w_3},$$

$$\begin{aligned}
\lambda_j(t) &= -\frac{3B_1B_2}{w_1+w_3}\frac{p_0(b(3r+4s)+r+s)}{b(3r+4s)+r+s}e^{-w_1t} \\
&+ \frac{((c_i+c_j+c_k+a)s+r(c_i+c_j+c_k))b}{b(3r+4s)+r+s}e^{-w_1t} \\
&+ \frac{a(r+s)}{b(3r+4s)+r+s}e^{-w_1t} - \frac{B_2B_4}{w_3}, \\
\lambda_k(t) &= B_{10}\frac{p_0(b(3r+4s)+r+s)}{b(3r+4s)+r+s}e^{-w_1t} \\
&- B_{10}\frac{((c_i+c_j+c_k+a)s+r(c_i+c_j+c_k))b+a(r+s)}{b(3r+4s)+r+s}e^{-w_1t} \\
&- \frac{B_2B_5B_6(B_3-B_4)}{w_3} - \frac{c_i+c_j+c_k-3a}{(s(4b+1)+r(3b+1))}.
\end{aligned}$$

By replacing λ_i and p with their expressions in equation (4.4), we get:

$$\begin{aligned}
q_i(t) &= \frac{w_1+w_3+3sbB_1B_2}{w_1+w_3}\Big(\frac{p_0(b(3r+4s)+r+s)}{b(3r+4s)+r+s}e^{-w_1t} \\
&+ \frac{a(r+s)}{b(3r+4s)+r+s}e^{-w_1t} \\
&- \frac{((c_i+c_j+c_k+a)s+r(c_i+c_j+c_k))b}{b(3r+4s)+r+s}e^{-w_1t}\Big) \\
&+ \frac{((c_i+c_j+c_k+a)s+r(c_i+c_j+c_k))b+a(r+s)}{b(3r+4s)+r+s} \\
&+ \frac{sbB_2B_3}{w_3} - c_i, \\
q_j(t) &= \frac{w_1+w_3+3sbB_1B_2}{w_1+w_3}\Big(\frac{p_0(b(3r+4s)+r+s)}{b(3r+4s)+r+s}e^{-w_1t} \\
&- \frac{((c_i+c_j+c_k+a)s+r(c_i+c_j+c_k))b}{b(3r+4s)+r+s}e^{-w_1t} \\
&+ \frac{a(r+s)}{b(3r+4s)+r+s}e^{-w_1t}\Big) \\
&+ \frac{((c_i+c_j+c_k+a)s+r(c_i+c_j+c_k))b+a(r+s)}{b(3r+4s)+r+s} \\
&+ \frac{sbB_2B_4}{w_3} - c_j,
\end{aligned}$$

$$
\begin{aligned}
q_k(t) = (1 - sbB_{10})\Big(&\frac{p_0(b(3r+4s)+r+s)}{b(3r+4s)+r+s}e^{-w_1 t} \\
&- \frac{((c_i+c_j+c_k+a)s + r(c_i+c_j+c_k))b}{b(3r+4s)+r+s}e^{-w_1 t} \\
&+ \frac{a(r+s)}{b(3r+4s)+r+s}e^{-w_1 t}\Big) + \frac{sbB_2(B_3-B_4)}{w_3} \\
&+ \frac{((c_i+c_j+c_k+a)s + r(c_i+c_j+c_k))b + a(r+s)}{b(3r+4s)+r+s} + \\
&- sb\frac{c_i+c_j+c_k-3a}{b(3r+4s)+r+s} - c_k,
\end{aligned}
$$

where

$$
1 - sbB_{10} = \frac{w_1 + w_3 + 3sbB_1B_2}{w_1 + w_3}.
$$

The proof is completed. □

4.2.2 Cooperative game version

In this section, we consider the differential game described above, when all players from set N are united into one coalition, i.e. in a three-person game, the coalition structure is $\{\{i,j,k\}\}$. Thus, this version of the game corresponds to full cooperation.

Theorem 4.2. *In a differential game with players' payoff functions* (4.2) *with given price dynamics* (4.1)*, when coalition structure* $\{\{1,2,3\}\}$ *is formed, if the Nash equilibrium in open-loop strategies exists, then the player's equilibrium strategy* $i = 1,2,3$ *satisfies the conditions:*

$$
\begin{aligned}
q_i = &\frac{s+r-w_2}{3}A_1 e^{w_2 t} \\
&+ \frac{(3a - \sum\limits_{j=1}^{3} c_j)(6bs+s+r) + (\sum\limits_{\substack{j=1 \\ j\neq i}}^{3} c_j - 2c_i)(3br+6sb+r+s)}{3(3br+6bs+r+s)},
\end{aligned}
$$

where

$$
\begin{aligned}
w_2 &= \frac{r - \sqrt{12brs + 24bs^2 + r^2 + 4rs + 4s^2}}{2}, \\
A_1 &= \frac{(3br+6sb+r+s)(3p_0 - c_i - c_j - c_k)}{(3br+6sb+r+s)(3bs+s+r-w_2)} \\
&\quad - \frac{(3a - c_i - c_j - c_k)(3bs+s+r)}{(3br+6sb+r+s)(3bs+s+r-w_2)}.
\end{aligned}
$$

Proof. We use the Pontryagin maximum principle. The Hamiltonian of coalition $\{i,j,k\}$, acting as a single player and maximizing the sum of players' profits, has the form:

$$H_{i,j,k} = p(q_i+q_j+q_k) - (c_iq_i+c_jq_j+c_kq_k) - \left(\frac{1}{2}{q_i}^2+\frac{1}{2}{q_j}^2+\frac{1}{2}{q_j}^2\right) + \lambda_{i,j,k}s(a-b(q_i+q_j+q_k)-p),$$

where $\lambda_{i,j,k}$ is an adjoint variable defined for coalition $\{i,j,k\}$. For simplicity, we introduce notation: $\lambda_{i,j,k}=\lambda$.

Maximizing Hamiltonian $H_{i,j,k}$ with respect to productions q_i, q_j, and q_k, we obtain the following system of equations:

$$\begin{aligned} p-c_i-q_i-sb\lambda=0,\\ p-c_j-q_j-sb\lambda=0,\\ p-c_k-q_k-sb\lambda=0, \end{aligned}$$

from where we find q_i, q_j, and q_k:

$$q_i = p-sb\lambda-c_i,\ i=1,2,3.$$

The system of differential equations for λ and p is written as follows:

$$\begin{aligned} \dot{\lambda} &= r\lambda - \frac{\partial H_{i,j,k}}{\partial p} = -3p+(r+s+3sb)\lambda+c_i+c_j+c_k,\\ \dot{p} &= -(3sb+s)p+3s^2b^2\lambda+sb(c_i+c_j+c_k)+sa. \end{aligned}$$

We rewrite the last system and get:

$$\begin{cases} \dot{p} &= -(3sb+s)p+3s^2b^2\lambda+sb(c_i+c_j+c_k)+sa,\\ \dot{\lambda} &= -3p+(r+s+3sb)\lambda+c_i+c_j+c_k. \end{cases}$$

We write this system of differential equations in a matrix form as

$$\begin{pmatrix}\dot{p}\\ \dot{\lambda}\end{pmatrix} = \begin{pmatrix}-3sb-s & 3s^2b^2n\\ -3 & r+s+3sb\end{pmatrix}\begin{pmatrix}p\\ \lambda\end{pmatrix}+\begin{pmatrix}sa+sb(c_i+c_j+c_k)\\ c_i+c_j+c_k\end{pmatrix}.$$

We find a solution of this system, i.e., λ and p, and to do this, we write the characteristic equation corresponding to the matrix of the system of differential equations, which has the form:

$$\begin{vmatrix}-3sb-s-w & 3s^2b^2n\\ -3 & r+s+3sb-w\end{vmatrix} = -w^2+rw+(3sb+s)(s+r)+3s^2b=0.$$

The characteristic equation has two roots:

$$w_{1,2} = \frac{r \pm \sqrt{\Delta}}{2},$$

where

$$\Delta = r^2 + 12sbr + 24bs^2 + 4s^2 + 4sr.$$

Obviously, $w_1 > w_2$, and moreover, $w_1 > 0$, $w_2 < 0$.

We obtain the solution of the system of differential equations:

$$\begin{aligned}
\lambda(t) &= A_2 e^{w_1 t} + A_1 e^{w_2 t} + \frac{3a - c_i - c_j - c_k}{3br + 6bs + r + s},\\
p(t) &= \Big(bs + \frac{s + r - w_1}{3}\Big) A_2 e^{w_1 t} + \Big(bs + \frac{s + r - w_1}{3}\Big) A_1 e^{w_2 t}\\
&\quad + \frac{(3a - c_i - c_j - c_k)(3bs + s + r)}{9br + 18bs + 3r + 3s} + \frac{c_i + c_j + c_k}{3},
\end{aligned}$$

where A_1 and A_2 are constants determined from the initial and limit conditions: $p(0) = p_0$ and $\lim_{x\to\infty} e^{-rt}\lambda(t) = 0$. From condition $\lim_{x\to\infty} e^{-rt}\lambda(t) = 0$ it follows that $A_2 = 0$, then the solution can be written as:

$$\begin{aligned}
\lambda(t) &= A_1 e^{w_2 t} + \frac{3a - c_i - c_j - c_k}{3br + 6bs + r + s},\\
p(t) &= \frac{3bs + s + r - w_2}{3} A_1 e^{w_2 t} + \frac{(3a - c_i - c_j - c_k)(3bs + s + r)}{9br + 18bs + 3r + 3s}\\
&\quad + \frac{c_i + c_j + c_k}{3}.
\end{aligned}$$

Given the initial condition $p(0) = p_0$, we find constant A_1:

$$\begin{aligned}
A_1 &= \frac{3p_0(3br + 6bs + s + r) - (3a - c_i - c_j - c_k)(3bs + s + r)}{(3br + 6bs + s + r)(3bs + s + r - w_2)}\\
&\quad - \frac{(3br + 6bs + s + r)(c_i + c_j + c_k)}{(3br + 6bs + s + r)(3bs + s + r - w_2)}.
\end{aligned}$$

Substituting A_1 into the solution, we get:

$$\begin{aligned}
p(t) &= \frac{3bs + s + r - w_2}{3} A_1 e^{w_2 t} + \frac{(3a - c_i - c_j - c_k)(3bs + s + r)}{9br + 18bs + 3r + 3s}\\
&\quad + \frac{c_i + c_j + c_k}{3},\\
\lambda(t) &= A_1 e^{w_2 t} + \frac{3a - c_i - c_j - c_k}{3br + 6bs + r + s}.
\end{aligned}$$

Substituting λ into the expressions for equilibrium productions, we obtain

$$\begin{aligned}
q_i &= \frac{s + r - w_2}{3} A_1 e^{w_2 t} + \frac{(3a - \sum_{\ell=1}^{3} c_\ell)(6bs + s + r)}{3(3br + 6bs + r + s)}\\
&\quad + \frac{(c_j + c_k - 2c_i)(3br + 6sb + r + s)}{3(3br + 6bs + r + s)},
\end{aligned}$$

where $i \neq j$, $i \neq k$, $j \neq k$, $i, j, k \in \{1, 2, 3\}$. The proof is complete. □

4.2.3 Case of partial cooperation

In this section, we consider the case when the formed coalition partition consists of two coalitions, there exist three such structures: $\{\{i, j\}, \{k\}\}$, $\{\{i, k\}, \{j\}\}$, and $\{\{j, k\}, \{i\}\}$. Taking into account the complexity of formulating the theorem defining the Nash equilibrium explicitly in such a game of two coalitions competing with each other, we present the formulation of the theorem for coalition structure $\{\{i, j\}, \{k\}\}$ and obtain the Nash equilibrium conditions with this structure.

Theorem 4.3. *For coalition structure $\{\{i, j\}, \{k\}\}$, in a differential game with players' payoff functions* (4.2) *and given price dynamics* (4.1)*, if there exists the Nash equilibrium in admissible open-loop strategies, then it is defined as follows:*

$$\begin{aligned} q_i &= p - c_i - sb\lambda_{ij}, \\ q_j &= p - c_j - sb\lambda_{ij}, \\ q_k &= p - c_k - sb\lambda_k, \end{aligned}$$

where p, λ_{ij}, and λ_k are the solutions to the system of differential equations:

$$\begin{aligned} \dot{p} &= -(3bs + s)p + 2s^2b^2\lambda_{ij} + s^2b^2\lambda_k + sb(c_i + c_j + c_k) + sa, \\ \dot{\lambda}_{ij} &= -2p + (r + s + 2sb)\lambda_{ij} + c_i + c_j, \\ \dot{\lambda}_k &= -p + (r + s + sb)\lambda_k + c_k \end{aligned}$$

with initial and limit conditions: $p(0) = p_0$, $\lim_{t\to\infty} e^{-rt}\lambda_{ij}(t) = 0$ and $\lim_{t\to\infty} e^{-rt}\lambda_k(t) = 0$.

Proof. In coalition $\{i, j\}$, firms maximize the coalition's total profit by choosing productions q_i and q_j. We use the Pontryagin maximum principle. The Hamiltonians for coalitions $\{i, j\}$ and $\{k\}$ are

$$\begin{aligned} H_{ij}(q_i, q_j, q_k, \lambda_{ij}, p) &= p(q_i + q_j) - c_iq_i - c_jq_j - \frac{1}{2}(q_i^2 + q_j^2) \\ &\quad + s(a - bQ - p)\lambda_{ij}, \\ H_k(q_i, q_j, q_k, \lambda_k, p) &= pq_k - c_kq_k - \frac{1}{2}q_k^2 + s(a - bQ - p)\lambda_k, \end{aligned}$$

where λ_{ij} and λ_k are the adjoint variables for coalitions $\{i, j\}$ and $\{k\}$ respectively.

Maximizing Hamiltonian H_{ij} with respect to productions q_i and q_j, as well as H_k with respect to production q_k, we obtain the following system of equations:

$$\begin{aligned} p - c_i - q_i - sb\lambda_{ij} &= 0, \\ p - c_j - q_j - sb\lambda_{ij} &= 0, \\ p - c_k - q_k - sb\lambda_k &= 0, \end{aligned}$$

whose solution is

$$q_i = p - c_i - sb\lambda_{ij}, \tag{4.5}$$

$$q_j = p - c_j - sb\lambda_{ij}, \tag{4.6}$$

$$q_k = p - c_k - sb\lambda_k. \tag{4.7}$$

We write down the system of differential equations with respect to λ_{ij}, λ_k, and p:

$$\begin{aligned} \dot{p} &= -(3bs + s)p + 2s^2b^2\lambda_{ij} + s^2b^2\lambda_k + sb(c_i + c_j + c_k) + sa, \\ \dot{\lambda}_{ij} &= -2p + (r + s + 2sb)\lambda_{ij} + c_i + c_j, \\ \dot{\lambda}_k &= -p + (r + s + sb)\lambda_k + c_k. \end{aligned}$$

Let us rewrite this system in a matrix form as

$$\begin{pmatrix} \dot{p} \\ \dot{\lambda}_{ij} \\ \dot{\lambda}_k \end{pmatrix} = \begin{pmatrix} -3sb - s & 2s^2b^2 & s^2b^2 \\ -2 & r + s + 2sb & 0 \\ -1 & 0 & sb + r + s \end{pmatrix} \begin{pmatrix} p \\ \lambda_{ij} \\ \lambda_k \end{pmatrix} + \begin{pmatrix} sa + sb(c_i + c_j + c_k) \\ c_i + c_j \\ c_k \end{pmatrix}$$

We find λ_{ij}, λ_k, and p, for this we write the characteristic equation, which looks like:

$$\begin{vmatrix} -3sb - s - w & 2s^2b^2 & s^2b^2 \\ -2 & r + s + 2sb - w & 0 \\ -1 & 0 & sb + r + s - w \end{vmatrix}$$

$$= -(3sb + s + w)(w^2 - (2r + 3sb + 2s)w + (r + 2sb + s)(r + sb + s))$$

$$+ s^2b^2(5r + 6sb + 5s - 5w) = 0.$$

It is difficult to write down the solution of this characteristic equation in a general case in an explicit form. Using, for example, the *Matlab* software, one can find the

unique admissible solution of this equation and express the solutions of a system of differential equations through this and other parameters of the system. When solving a system of differential equations, we use the initial and limit conditions: $p(0) = p_0$, $\lim_{t\to\infty} e^{-rt}\lambda_{ij}(t) = 0$ and $\lim_{t\to\infty} e^{-rt}\lambda_k(t) = 0$. After finding solutions, we substitute λ_{ij}, λ_k, and p into expressions (4.5), (4.6), and (4.7), and obtain the Nash equilibrium strategies. □

Remark 4.1. *Conditions for Nash equilibrium in the case of coalition structures* $\{\{i,k\},\{j\}\}$ *and* $\{\{j,k\},\{i\}\}$ *can be found similar to Theorem 4.3. Solution of a system of differential equations from the proof of Theorem 4.3 was found using the Matlab program,that is presented in Section 4.4, which considers a numerical example.*

4.3 Stability of coalition structures

In our model, the coalition structure is given exogenously, i.e., the players do not participate "actively" in forming a coalition structure. But even if the structure is given, the problem of its stability arises. By stability, it is natural to understand a stable structure at which no firm would prefer to leave its coalition in order to join another one, or become an individual player. Although firms in a coalition choose strategies that maximize the total coalition's profits, they can compare their own profits in these coalitions to decide which coalition is more preferable for them [5].

We give a definition of a stable coalition structure based on the Nash equilibrium principle, i.e. on the fact that it is nonprofitable for any player to individually deviate from a stable structure, i.e. to move to other coalitions or become an individual player.

Definition 4.2. *Coalition structure* $\pi = \{B_1, \ldots, B_m\}$ *is said to be stable in a game with nontransferable payoffs if the following inequality holds for any player* $i \in N$*:*

$$J_i^{\pi} \geq J_i^{\pi'} \text{ for all } B_j \in \pi \cup \emptyset,\ B_j \neq B(i).$$

Here J_i^{π} *and* $J_i^{\pi'}$ *are the payoffs of player* i *in a game with given coalition structure* π *and* π' *respectively, where* $\pi' = \{B(i)\backslash\{i\}, B_j \cup \{i\}, \pi_{-B(i)\cup B_j}\}$, $B(i)$ *is a coalition from structure* π *which player* i *belongs to.*

4.4 Numerical example

To illustrate the theoretical results obtained in the previous sections, we consider a differential game described above between three firms from set $N = \{i, j, k\}$. It is assumed that firms can form any coalition structure: $\{\{i, j, k\}\}$ (cooperative version), $\{\{i\}, \{j\}, \{k\}\}$ (noncooperative version), $\{\{i, j\}, \{k\}\}$, $\{\{i, k\}, \{j\}\}$ and $\{\{j, k\}, \{i\}\}$ (partially cooperative version).

We use the following parameters for numerical simulations:

p_0	c_i	c_j	c_k	b	r	s	a	n
0.5	0.4	0.2	0.3	0.2	0.3	0.5	0.7	3

Applying Theorems 4.3.1, 4.3.2, and 4.3.3, we find equilibrium price $p(t)$ and strategies $q_i(t)$, $q_j(t)$, and $q_k(t)$ for all coalition structures. The result in graph form is shown in Fig. 4.1.

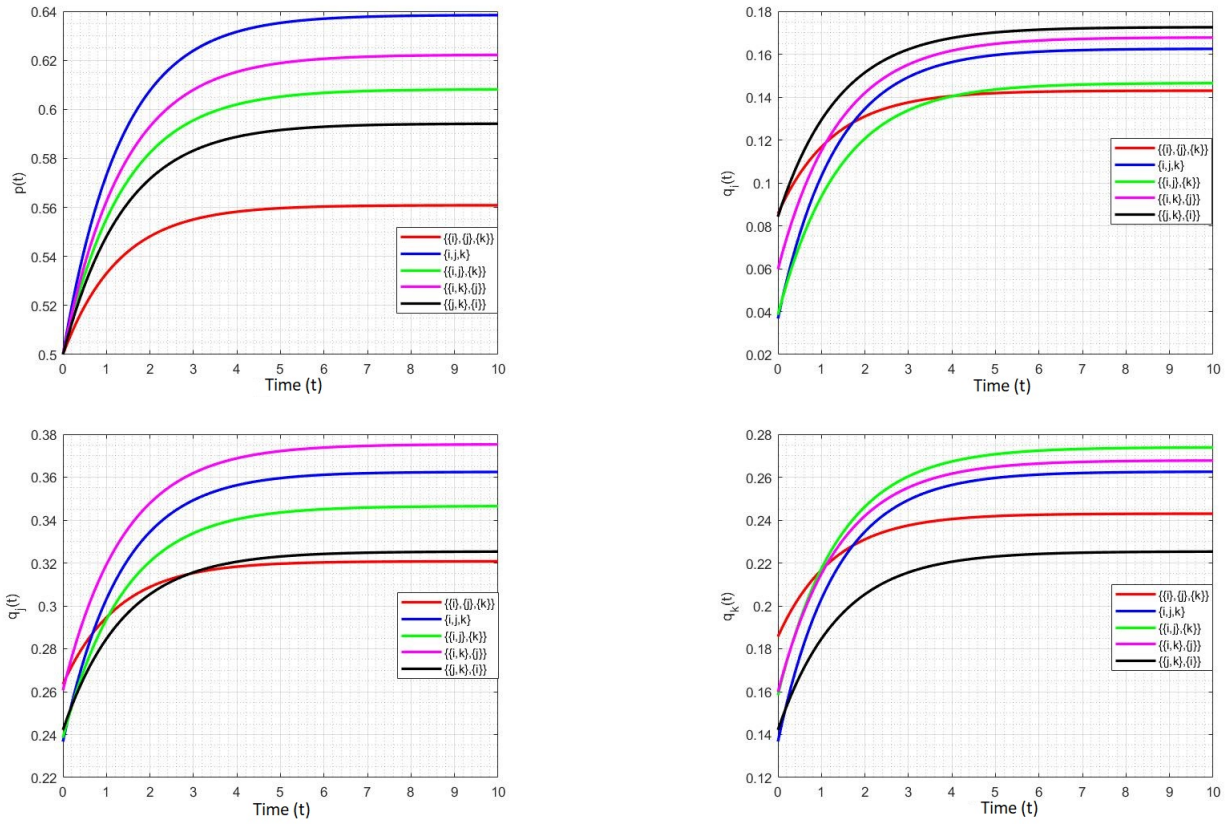

Figure 4.1: Equilibrium prices and firms' productions for various coalition structures

The profits of firms i, j, and k are calculated by substituting equilibrium $p(t)$, $q_i(t)$, $q_j(t)$, and $q_k(t)$ from Theorems 4.3.1, 4.3.2, and 4.3.3 into the firms' payoff functions (4.2). The firms' payoffs are given in Table 4.1.

Table 4.1: Firms' payoffs under various coalition structures

	J_i	J_j	J_k
$\{\{i\},\{j\},\{k\}\}$	0.0346	0.1952	0.0993
$\{\{i,j,k\}\}$	0.0600	0.2593	0.1430
$\{\{i,j\},\{k\}\}$	0.0460	0.2273	0.1237
$\{\{i,k\},\{j\}\}$	0.0557	0.2473	0.1344
$\{\{j,k\},\{i\}\}$	0.0467	0.2178	0.1123

The analysis of the obtained results shows (see Table 4.1) that for all firms coalition structure $\{\{i,j,k\}\}$ is preferable, since the payoffs of all firms are greater with this coalition structure than with any other one. Obviously, this coalition structure is stable in accordance with Definition 4.2, since it is unprofitable for any player to deviate from this coalition structure, i.e. to become an individual player.

The analysis of equilibrium prices with various coalition structures shows that the lowest price is formed under full competition, i.e. with coalition structure $\{\{i\},\{j\},\{k\}\}$. It means that this structure is the most preferable for consumers, followed by structures $\{\{j,k\},\{i\}\}$, $\{\{i,j\},\{k\}\}$, $\{\{i,k\},\{j\}\}$, $\{\{i,j,k\}\}$ in order of increasing price. As expected, $\{\{i,j,k\}\}$ coalition structure or full cooperation is the least preferred scenario for consumers. Table 4.2 shows price limits with different coalition structures. Of course, it is more profitable for firms to have coalition structure $\{\{i,j,k\}\}$, if we talk about firm profits, and consumers prefer competition, i.e. coalition structure $\{\{i\},\{j\},\{k\}\}$, when the lowest price is formed for them on the market.

Table 4.2: Equilibrium price limits $\bar{p} = \lim_{t\to\infty} p(t)$ for various coalition structures

	$\{\{i\},\{j\},\{k\}\}$	$\{\{i,j,k\}\}$	$\{\{i,j\},\{k\}\}$	$\{\{i,k\},\{j\}\}$	$\{\{j,k\},\{i\}\}$
$\bar{p}$	0.5609	0.6384	0.6081	0.6222	0.5941

4.5 Conclusion to Chapter 4

This chapter proposes a model of competition in the market of manufacturers of vaccines or other products, when the product price has the property of the so-called "memory", i.e. it is dynamically formed not only by demand, but also by the previous price value. The model is represented by a differential game of infinite duration, where the players' strategies are production volumes. It is assumed that players-

firms can form any coalitions, i.e., not only a grand coalition, but also coalitions of smaller sizes. In this chapter, the Nash equilibrium is found in a game with a given coalition structure. The chapter considers the case of nontransferable utilities, i.e. players cannot redistribute payoffs in cooperation. A numerical example demonstrates theoretical results and analyzes the stability of coalition structures. Finally, we draw conclusions about which structures are preferable for consumers and firms.

Conclusion

The thesis is devoted to mathematical and game-theoretic modeling of malaria spread in human population (as well as in mosquito population in Chapter 2), economic interaction of vaccine companies, and creation of models for predicting malaria disease based on available statistical data. The paper proposes epidemiological models of the $SEIR$ type of vector-borne disease (malaria). For each of the presented models (Chapters 1 and 2), the region of acceptable values was investigated, the basic reproductive number R_0 was calculated, some equilibria were determined (the equilibrium when the disease is absent in the population and the endemic equilibrium), the stability of equilibria was analyzed, and numerical modeling based on the obtained theoretical results was conducted, the impact of vaccination on malaria spread in human population was studied.

Chapter 3 presents two models of malaria spread for practical application and disease forecasting. The first model is based on the classical SIR model and modified to describe the development of malaria in Senegal using annual data. The second model is based on the principle of dynamic balance of an epidemiological process and takes into account when making forecasts generated dynamic trends of stochastic values of a percentage increase in the total number of diseased people and assumptions about the stationary or nonstationary nature of a change in dynamic balance characteristics. The latter model is usually used for forecasting when daily, weekly or monthly data are available, i.e. a time interval between observations is less than the duration of the disease. But the modified model was applied to annual data, and the malaria disease forecast based on these data turned out to be quite accurate, especially compared to the forecast made using the modified SIR model. The estimates obtained for the selected forecast intervals demonstrate a higher accuracy of balance model forecasts for estimating future values of active cases and a size of a recovered part of the population.

Chapter 4 proposes a model of competition in the market of vaccine manufacturers

or other products, when the product price has the so-called "property of memory", i.e. it is dynamically formed not only by demand, but also by a previous price value. The model is a differential game of infinite duration, where the players' strategies are production volumes. It is assumed that players-firms can form any coalitions, i.e., not only a grand coalition, but also coalitions of smaller sizes. In this paper, we find the Nash equilibrium in a game with a given coalition structure. The paper considers a case of nontransferable utilities, i.e. players cannot redistribute payoffs received from cooperation. A numerical example demonstrates the theoretical results obtained, analyzes the stability of coalition structures, and draws conclusions about which structures are preferable for buyers and firms.

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Appendix A. Background information on malaria, its treatment and malaria vaccines

Malaria is a parasitic disease carried by mosquitoes. It usually presents with flu-like symptoms and can lead to serious complications or even death. In tropical areas, malaria has a mortality rate that is unmatched by any other disease. In this regard, an important task is the application of effective methods of treatment, as well as the implementation of existing preventive measures for the population living in areas endemic for malaria. At the same time, scientific research is aimed at developing new preventive and therapeutic methods, including vaccines, that will make it possible to eradicate this disease.

Malaria is caused by a parasite of the genus *Plasmodium*, which is primarily transmitted from person to person through the bite of a female *Anopheles* mosquito. Plasmodium can also be passed from mother to child during late pregnancy or, in exceptional cases, through blood transfusion.

There are five different *Plasmodium* species that can infect humans: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium knowlesi* [43]. They differ in the geographical area they inhabit and in the nature of the symptoms they cause.

1. *P. falciparum* is the most common species in the world and the cause of most malaria-related deaths. However, its impact varies by region: for example, it was responsible for 99.7% of suspected malaria cases in Africa in 2018, but only half of the cases were in Southeast Asia.

2. *P. vivax* is predominant in Central and South America, where it is responsible for 75% of cases. This species is also present in Asia and, to a lesser extent, parts of Africa. *P. vivax* is significantly less virulent than *P. falciparum*, but the number of deaths associated with it has been increasing in recent years.

3. *P. ovale* is found mainly in West Africa. The symptoms it causes are usually mild.

4. *P. malariae* is present worldwide but rare.

5. *P. knowlesi* is common among monkeys. But for the past few years, it has been causing malaria in humans in Southeast Asia. Difficult to diagnose, it poses a potentially serious hazard to the treatment of the disease.

Malaria is said to be as old as the world [44]. A papyrus found in Luxor dating back 15 centuries mentions an infection that closely resembles an attack of malaria. analysis ADN of the body of Tutankhamun (born about 1345, died about 1327 our era) showed that at the time of his death he suffered from malaria. The disease is believed to have originated in marshy areas and areas with polluted air, hence the name malaria, derived from the Italian malaria (bad air). The disease has raged for a long time in Europe, and has caused damage comparable to that which it causes today in Africa. In the XVI century, the conquest of the New World and the slave trade began. European slave traders take African slaves suffering from malaria to America. In 530, the Spanish Jesuit Don Francisco Lopez discovered the healing properties of cinchona bark from Peru, already used by the Indians to treat fevers, in the form of a powder brought to Europe. In 1820, two French pharmacists, Pelletizer and Caventou, isolated quinine from the bark of the cinchona tree, which became the first effective cure for malaria. In 1880, the French physician Alphonse Laveran was the first to discover the malaria parasite *falciparum* in the erythrocytes of patients under a microscope. In 1897, Briton Ronald Ross also made an important discovery: malaria is transmitted to humans through the bite of an Anopheles mosquito. Until the beginning of the 20th century, quinine remained the only antimalarial drug. Chloroquine and other synthetic antimalarial appeared in the early 1940s. In parallel with this, in order to destroy anopheles, their habitats are massively sprayed with insecticides. In 1955, with the first victories against the disease, the World Health Organization (WHO) launched a global program to eradicate malaria, but the parasites that cause it became increasingly resistant to treatment. In 2001, the World Health Organization recommended a new therapy, ACT, which combines the drug artemisinin, already used by the Chinese in the fourth century, with one or two other antimalarial drugs. ACT is highly effective, but resistance to this new therapy emerged early in Asia.

Malaria, which kills over 500,000 people every year, is the world's leading parasitic disease [42]. It affected 198 a million in 2013, most of them in poor countries. Malaria affects about a hundred countries, especially in tropical areas. Africa alone accounts for 90% of malaria cases, well ahead of Asia and the Middle East with more than 20 a million cases, with Nigeria and the Democratic Republic of the Congo suffering the heaviest losses. Fortunately, malaria deaths worldwide, especially in Africa, have been cut in half over the past ten years. These achievements are due to several factors: prevention, distribution of mosquito nets, spraying of insecticides, preventive treatment of pregnant women and, above all, treatment with *ACT* therapy, based on artemisinin, obtained from *Artemisia annua*, used in traditional Chinese medicine. Despite the fact that the number of sick children has also been halved, children are still the main victims of this disease. Every minute a child under 5 dies of malaria. In 2013, 79 out of 88 countries where the malaria parasite is rampant included the latest *ACT* medicines in their health programs. Access to health care and screening is a real problem in the fight against this disease in Africa, 70% of patients could be treated with *ACT* antimalarial drugs distributed in public health facilities. But since most children with fever never see a doctor, only 26% of them received *ACT* in 2013. *ACT*, the combination of artemisinin with one or two other drugs, like its predecessors, faces parasite adaptation. Recently, cases of resistance to *ACT* drugs have appeared in Cambodia, Laos, Thailand, Myanmar, the former Burma and Vietnam.

The life cycle of malaria describes the various phases in the development and spread of this mosquito-borne infectious disease caused by various protists known as Plasmodium, and five varieties of Plasmodium are capable of infecting humans; *Plasmodium falciparum* tends to cause the most severe infections. Malaria infection in individuals is determined by several factors such as temperature, climate, environment, etc. Some details are omitted from the description of the malaria cycle. It is worth saying that malaria infection in the human population begins when sporozoites enter the bloodstream of an infected female mosquito. The sporozoites migrate to the liver, and after a period (sometimes weeks, sometimes months) they enter the bloodstream in the form of gametocytes, which the mosquito first receives upon contact with an infected person. During the developmental cycle of the mosquito, the introduced gametocytes become gametes, which first develop into zygotes, then into motile ookinetes, which penetrate the mosquito intestine and re-

lease a large number of sporozoites. This cycle can be schematized as [30] shown in Fig. 4.2.

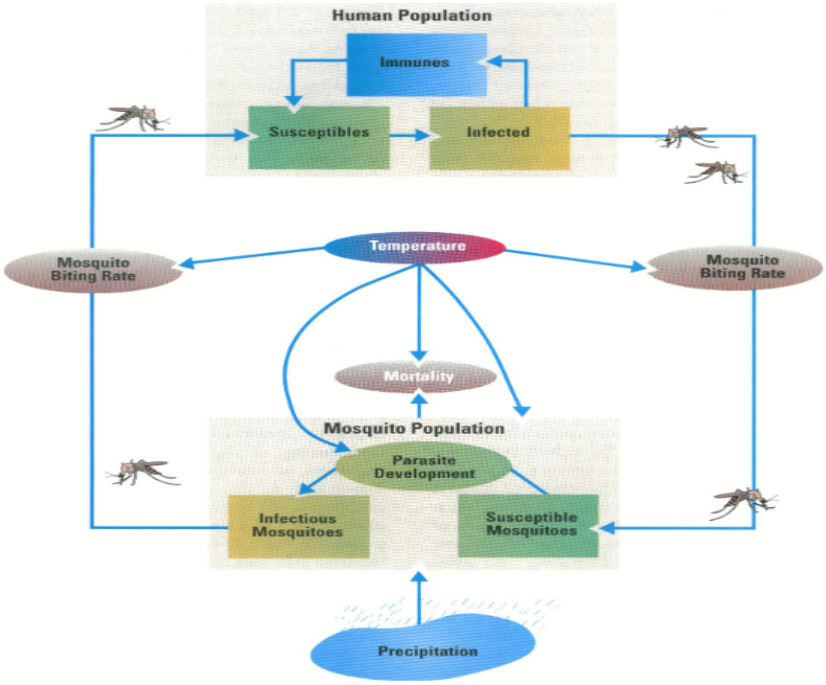

Figure 4.2: Diagram of the main population processes and spread rates involved in the life cycle of the malaria parasite (figure borrowed from [30]).

Much research has been done in recent years and progress has been made in understanding host-parasite-vector interactions and their biology. However, it is worth bearing in mind that the complexity of the parasite life cycle, intense ecological and social interactions, evolutionary use of drugs and control measures, drug resistance of the parasite, unforeseen effects of climate change, and population migration between endemic and non-endemic areas contribute to the enormous spread of morbidity and mortality, to caused by this disease, which also poses new challenges for researchers and public health professionals.

Anopheles, mosquitoes that live in the tropics, are only a carrier of malaria, the true culprit of which is the parasite it carries, Plasmodium. The female *Anopheles* bites at night as it feeds on human blood. If its prey is already infected, the mosquito sucks up the blood of many parasites. Once in the mosquito's stomach, the parasites multiply by dividing and migrate to the salivary glands. During the bite, the parasites infect new victims through the blood. In the human body, plasmodium begins a phase of multiple mutations: sporozoites turn into trophozoites, then into a schizont, then into merozoites, and finally into gametocytes. All these metamorphoses allow him to avoid the obstacles created by the immune system of

these victims. The parasite's first destination is the liver, which the parasite travels to via the bloodstream. The parasite then infects the liver cells and multiplies until the liver cells rupture and release the parasites into the bloodstream, causing the first symptoms of chills. Then the parasites invade the erythrocytes, multiply rapidly in them, causing them to rupture. A new generation of Plasmodium fills with blood, which, in turn, can be sucked out by a new mosquito. The cycle is complete.

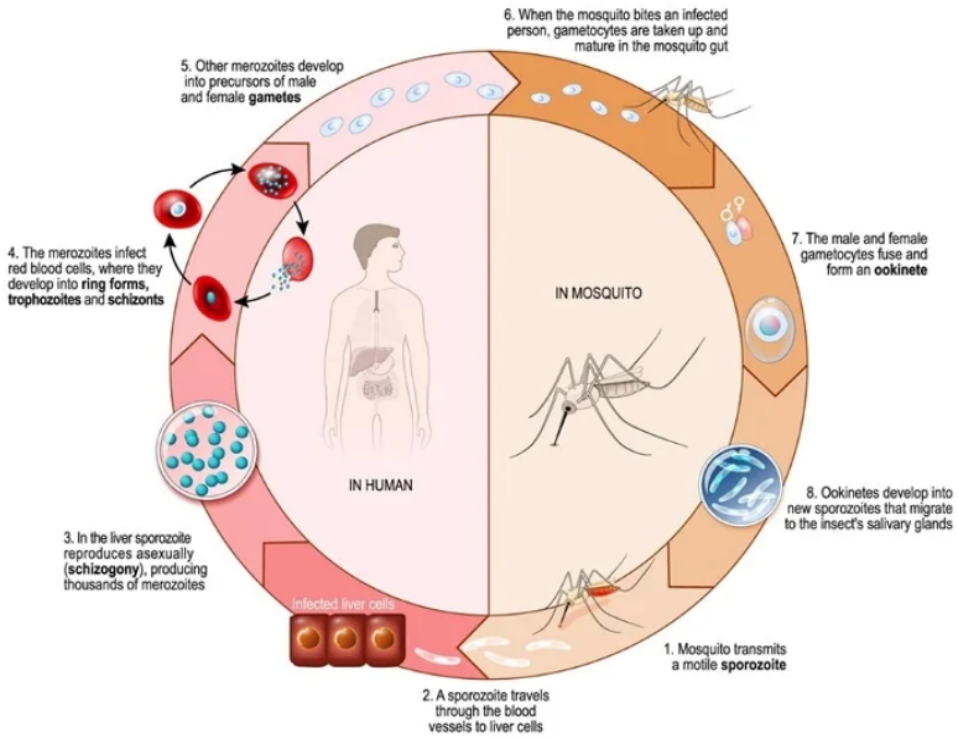

Figure 4.3: Life cycle of the malaria parasite [40].

The rupture of red blood cells causes an attack of fever lasting several hours, characteristic of malaria: chills, fever and sweat follow each other. These outbreaks of fever recur every two to three days. In the case of plasmodium *falciparum*, malaria can affect other organs such as the brain and progress to severe and even fatal forms. Populations that have had the disease multiple times become partially immune to it. Young children with developing immune defenses and pregnant women with altered immune systems during pregnancy are at the greatest risk of severe malaria and even death.

Anopheles is a mosquito that lives in regions with a warm and temperate climate. There are about 600 species, 70 of which can transmit malaria. Most male mosquitoes mainly feed on flower nectar and fruit juices and never bite. The female,

for her part, needs to take a blood meal before each egg laying. A mosquito usually lives from two weeks to a month. Its lifespan depends on climatic conditions, and it mates only once. After mating, the reserve of spermatozoa deposited in the body of the female ensures the fertilization of all eggs. She lays an average of 90 of eggs once every two to three days. Usually the female bites at night (from dusk to dawn). Eggs are laid in stagnant or moving water (maybe a fairly small pool) depending on the species. These eggs hatch into aquatic larvae that remains horizontally on the surface of the water. These larvae feed on unicellular algae. Their evolution will lead to the emergence of adult flying insects. Depending on climatic conditions, the duration of development from the egg to the adult stage can vary from one to three weeks.

To test for malaria, just apply a drop of blood taken from the tip of your finger to the strip, with this quick tester, doctors can act immediately. A more accurate but more difficult diagnosis under a microscope allows the type and number of parasites to be determined. If left untreated within 24 hours, malaria can develop into a severe or even fatal infection. The malaria parasite is usually resistant to single drug treatment. The most effective treatment is a combination of several drugs based on the active ingredient artemisinin, known to Chinese medicine for over 2000 years. The combination of an artemisinin derivative with other drugs allows you to better resist the parasite. These are therapy drugs ACT. They have been in use since the early 2000s. In general, ACT drugs are well tolerated, reduce transmission, and provide a cure within three days. However, a disturbing trend has been observed in recent years: the emergence of cases of malaria resistant to artemisinin derivatives. Most of these cases were reported in Cambodia, Thailand and Myanmar. Resistance to ACT may pose a serious threat in endemic areas, as no other antimalarial drugs will be available for at least five years. Prevention of malaria mainly involves the use of insecticides in homes and the use of treated mosquito nets. Since 2011, seasonal malaria prophylaxis for children aged 3 months to 5 years has also been shown to be effective in the Sahel. The same type of chemotherapy prophylaxis given to pregnant women protects mother and baby.

Malaria vaccine research has been marked by the development of a vaccine against *P. falciparum (RTS,S or Mosquirix)*, which is starting to be implemented and evaluated in some African countries. This vaccine targets one of the parasite proteins present on its surface during the erythrocyte phase (sporozoite). With a vaccine ef-

ficacy of about 30%, its effect remains limited: in order for vaccines to be effective, the antibodies they produce must be present in the blood in very high concentrations. However, this only occurs in the first weeks after vaccination. Then their level gradually decreases and after about a year it becomes insufficiently effective.

Other vaccines are under development at very early stages. While not all the approaches under consideration lead to the development of a universal vaccine, they should nonetheless provide new insights into the determinants of malaria immunity, which in turn will lead to better vaccine designs. Among them are subunit vaccines aimed at blocking a specific protein of the parasite, such as *RTS,S*. One of the most promising vaccines is one that targets the *PfRH5* protein, which allows the parasite to enter and survive in red blood cells. Others, intended for pregnant women, are aimed at stimulating a response against parasitic proteins that interfere with the functioning of the placenta [44].

A more classic vaccine, called "live attenuated" is *PfSPZ*. It is based on an injection containing thousands of parasites rendered inactive to induce the immune system to produce an intense response, especially a cellular one (mediated by $TCD8$ lymphocytes). However, this promising approach faces a major problem: the parasites used to produce the vaccine must be isolated from infected mosquitoes, and injection must be done intravenously, making it difficult to carry out on a large scale. Based on the same principle, a strategy that combines the simultaneous injection of a live parasite and antimalarial drugs offers an interesting model for understanding the immune mechanisms implemented by the human body.

Finally, vaccines are being developed from genetically engineered parasites that have mutated several key proteins to make them unable to enter or replicate in target cells. They would allow us to consider the possibility of developing an adapted immune response in the host.

Appendix B. Determination of the basic reproductive number

This section describes for reference the most commonly used methods for determining the basic reproductive number.

Anderson and May Method.

The number R_0 is determined by the formula:

$$R_0 = \beta C D,$$

where β — the probability of transmission of the disease;
C — the number of contacts between an infected and a healthy person per unit of time;
D — the average time of the infectious period.

The Bokh Method (1886).

Let $F(a)$ be the probability of an individual surviving to age a, and $\beta(a)$ be the birth rate in the population, then $\int_0^\infty \beta(a)F(a)\,\mathrm{d}a$ — the number of births generated by this individual during his lifetime.

This definition given by Bokh for the field of demography can be adapted to epidemiology [52].

Let $F(a)$ be the probability of infection before age a (i.e. the age of infectivity) and $\beta(a)$ − the rate of transmission, then R_0 determines the number of newly infected:

$$R_0 = \int_0^\infty F(a)\beta(a)\,\mathrm{d}a.$$

.

Next generation matrix method.

The system under consideration is:

$$\dot{x} = f(x),$$

where $x = (x_1, \ldots, x_n)^T$ is the state of the system.

The population is divided into n parts, the number of individuals in the i-th part is determined by the number x_i. Parts of a population referred to its subgroups, such as susceptible infected, vaccinated, etc.

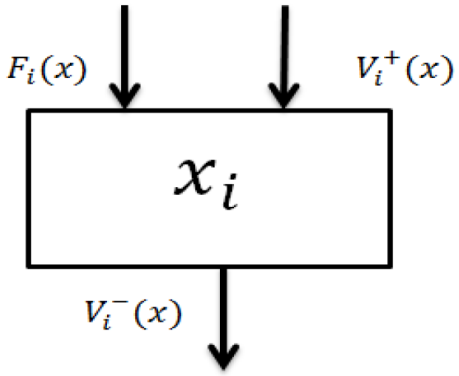

Figure 4.4: Part of the i population. Equilibrium of entry and exit

Let's analyze what goes in and out of each part (see fig. 4.4):

1. Denote by $\mathcal{F}_i(x)$ the rate at which new infected people appear.
2. $\mathcal{V}_i^+(x)$ denotes an incoming flow of individuals that come from other parts of the population for some other reason (movement, restoration, etc.).
3. Denote by $\mathcal{V}_i^-(x)$ the rate of those who leave the i-th part of the population (for example, mortality, change in epidemiological status, etc.).

Finally, we get:

$$\dot{x} = \mathcal{F}_i(x) + \mathcal{V}_i(x), \qquad \mathcal{V}_i(x) = \mathcal{V}_i^+(x) + \mathcal{V}_i^-(x).$$

Let X_S denote the disease-free state, i.e. $X_S = \{x \in \mathbf{R^n}/x_i = 0 \quad i = 1, \ldots, p\}$, where parts of the population $1, \ldots, p$ consist of infected or infected individuals.

Let's make the following assumptions:

1. $x \geq 0, \quad \mathcal{F}_i(x) \geq 0, \quad \mathcal{V}_i^+(x) \geq 0, \quad \mathcal{V}_i^-(x) \geq 0.$
2. If $x_i = 0$, then $\mathcal{V}_i^-(x) = 0$. If there are no individuals in a certain part of the population, nothing comes out of it.
3. If $i > p$, then $\mathcal{F}_i(x) = 0$. Parts of the population with an index greater than p are "uninfected".

4. If $x \in X_S$, then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, \ldots, p$. If there are no carriers of the virus in the population, then only new "infected" ones can appear.

Calculate the Jacobian at the equilibrium point without illness x^*:

$$J(x^*) = D\mathcal{F}(x^*) + D\mathcal{V}(x^*),$$

where

$$D\mathcal{F}(x^*) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}$$

and

$$D\mathcal{V}(x^*) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}.$$

In this case, $F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}\right]_{1 \le i,j \le p}$ And $V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}\right]_{1 \le i,j \le p}$.

Here $F \geq 0$ is a positive definite matrix with positive diagonal entries.

Then R_0 is defined as follows:

$$R_0 = \rho(-FV^{-1}),$$

where ρ is the spectral radius.

Appendix C. Senegal malaria database 2000-2021

Year	Suspected Cases	Tested cases	No. of infected	No. of deaths	No. of recovered
2021	2090743	2001032	536850	399	536451
2020	2100345	2012507	445313	373	444940
2019	2010398	2005860	354708	260	354448
2018	2096124	2090323	530944	555	530389
2017	2035693	2033022	395706	284	395422
2016	1559054	1552322	349540	325	349215
2015	1421221	1411390	492253	526	491727
2014	727918	702601	268912	500	268412
2013	867157	757697	366687	815	365872
2012	666101	555724	280241	649	279592
2011	633380	579223	274119	472	273647
2010	721687	661503	330331	553	329778
2009	584896	497716	165933	574	165359
2008	737694	487398	241926	741	241185
2007	1454660	587160	118332	1935	116397
2006	893682	674094	48070	1678	46392
2005	693651	543987	33160	1587	31573
2004	653098	384908	22234	1524	20710
2003	493087	243201	26865	1602	25263
2002	549027	320903	14425	1226	13199
2001	503486	340582	12920	1515	11405
2000	703491	470984	44959	1275	43684