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PARAMETERS' ESTIMATION, SENSITIVITY ANALYSIS AND MODEL UNCERTAINTY FOR AN INFLUENZA A MATHEMATICAL MODEL: CASE OF MOROCCO

BIDAH SARA[1], ZAKARY OMAR[1,*], TRIDANE ABDESSAMAD[2], RACHIK MOSTAFA[1], FERJOUCHIA HANANE[1]

[1]Laboratory of Analysis, modeling and simulation, Department of mathematics and computer sciences, Faculty of sciences Ben M'Sik, University Hassan II of Casablanca, Morocco

[2]Department of Mathematical Sciences, United Arab Emirates University, Al Ain, United Arab Emirates

Abstract. In this paper, we consider a SEIS model type compartmental model to explore the evolution of the Influenza epidemic in Morocco. To consider a more realistic model we consider the seasonality of parameters, by considering time-dependent infection rate, time-dependent recovery rate, and time-dependent intervention rate. The next-generation matrix method is used to compute the threshold of equilibria's stability R_0. Based on real data of Influenza epidemic A infections in Morocco from the month of December 2018 to the month of March 2019 published by the Influenza Laboratory Surveillance Information system, we estimate the model parameters. In order to identify the most influential parameter in the proposed model, we carry out the local sensitivity analysis. We calculate sensitivity indices based on the estimated parameters which identify the most influential parameters. We perform also the uncertainty analysis to determine the relationship between the different parameters of the model.

Keywords: influenza A; pandemic; mathematical model; estimation of parameters; sensitivity analysis; model uncertainty.

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*Corresponding author

E-mail address: zakaryma@gmail.coml

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1. INTRODUCTION

Influenza is an infectious disease of birds and mammals caused by RNA viruses of the family the influenza viruses. The most common symptoms are chills, fever, runny nose, sore throat, muscle pain, headache (often severe), coughing, weakness, and general discomfort. Although it is often confused with other influenza-like illnesses, especially colds, flu is an even more severe disease. Influenza may cause nausea and vomiting, especially in children [1].

Usually, the flu is transmitted through the air by coughing or sneezing, which creates aerosols that contain the virus. Influenza can also be transmitted through direct contact with bird droppings or nasal secretions, or by contact with contaminated surfaces. Airborne aerosols are believed to cause most infections, although the most important transportation is not entirely clear. Influenza is a seasonal epidemic disease, which appears every year due to a lack of awareness of basic knowledge [1].

Seasonal influenza (or "flu") is most often caused by type A or B influenza viruses. Influenza A viruses are further classified into subtypes according to the combinations of the hemagglutinin (HA) and the neuraminidase (NA), the proteins on the surface of the virus. Currently circulating in humans are subtype A(H1N1) and A(H3N2) influenza viruses. The A(H1N1) is also written as A(H1N1)pdm09 as it caused the pandemic in 2009 and subsequently replaced the seasonal influenza A(H1N1) virus which had circulated prior to 2009. Only influenza type A viruses are known to have caused pandemics [2].

Influenza A (H1N1) virus is a highly contagious and pathogenic fatal disease. A novel virus named influenza A (H1N1) virus was identified in Mexico and the USA in April 2009 and the world health organization (WHO) declared it as a pandemic on June 11, 2009 [3]. After the World Health Organization announced the epidemiological level 6 of this new strain, the Ministry of Health in Morocco launched case-based surveillance for influenza A (H1N1) infection, in addition to the Influenza Laboratory Surveillance Information.

For new infectious diseases, setting epidemiological parameters can help in decision-making. The main parameter of a new infectious disease is the primary reproductive number (R_0), which is defined as the average number of secondary cases resulting from one primary state throughout the entire infection period in a fully susceptible population [4].

Epidemiological models are useful for comparing the effects of prevention or control measures. One of the most important concerns about any infectious disease is its ability to invade the population. Many epidemiological models have a disease-free equilibrium (DFE) where the population remains in the absence of disease. R_0 directly determines the epidemic growth rate and the final number of infected people and is a dominant factor that must be taken into account in optimal policymaking. In fact, most models typically consider R_0 as a threshold parameter, so that if $R_0 < 1$, DFE is locally asymptotically stable, and disease cannot invade the population, but if $R_0 > 1$, DFE is unstable and invasion is always possible, Thus, the stability of epidemiological models can be analyzed with the help of R_0 [4]. There are a few methods available to estimate R_0. For determination of the basic reproductive number, one of the best approaches is the Next Generation Matrix method [4, 5, 6].

Mathematical models play an important role in the investigation and the control of different phenomena [7, 8], such as the propagation of human infectious diseases, which allowing health policy-makers to predict the impact of particular vaccine and treatment programs or to derive more efficient strategies based on different mathematical methods.

In [10], Kermack and McKendrick devised the Susceptible-Infected-Removed (SIR) model which has presented an interesting contribution to the mathematical theory of epidemics. The mathematical SIR model is in the form of three compartments: susceptible, infected, or removed. Susceptible populations are healthy and do not carry the epidemic but can contract it from infected individuals which carry the infection and can pass it to susceptible hosts, while the removed people are no longer infected and acquire immunity from future contagion.

Susceptible-Infected-Susceptible (SIS) [15] epidemic models have been applied to situations in which it is supposed that an infected population could move immediately to the susceptible compartment after being recovered from an infection due to the lack of immunization. Susceptible-Exposed-Infected-Susceptible (SEIS) epidemic models have been applied to situations in which it is supposed that there is a period of incubation of the infection and after that, an infected individual could move to the susceptible compartment again after being recovered from an infection due to the lack of immunization like the case of the seasonal Influenza. This kind

of compartmental model is also useful to model the evolution of many phenomena in different situations, see as examples, subjects treated in [17, 18, 19, 20, 21].

The first work that generalizes the compartments-based models which describe and control the evolution of pandemics and epidemics within a geographical area, is done by Zakary et al in [11, 12], where the authors developed a new modeling approach to describe the Spatio-temporal spread of diseases and suggested several strategies of control by adopting different generalized models in discrete and continuous-time [13, 14, 16, 22, 23, 24, 9].

People infected with A (H1N1) passes through an incubation period where they are not infectious and do not show any symptoms. The period of incubation for A (H1N1) virus is 1 to 4 days and the infectious period case is defined as 1 day prior to the onset of symptoms to 7 days after onset [25]. Therefore, and based on all these considerations, we consider in this paper a compartments-based mathematical SEIS model to describe the evolution of the Influenza pandemic in Morocco. First, we present the different parameters of the model and the interactions between its states. We introduce the seasonality of this disease by considering time-dependent parameters such as the infection rate, the recovery rate, and the control policy. Second, we perform the stability analysis of the equilibria based on values of the threshold R_0 which is calculated with the help of the next-generation matrix method. To validate the model we propose here, our study is based on real data of Influenza A viruses in Morocco [28]. Then we estimate the model's parameters by matching the model's outputs with the actual data. Next, we perform a sensitivity analysis to show the most important parameter in changing the basic reproductive number R_0 and to determine the most influential parameter taking into account the seasonality of parameters, so we define seasonal sensitivity indicators to show that the parameters have an impact period which makes the disease more severe in some months. Finally, we implement the model uncertainty to check and verify the performance of the parameters' estimation.

2. THE MODEL

We formulate the transmission dynamics model for a single outbreak of the Influenza epidemic in a homogeneously mixing population in Morocco. We divide the population into three main epidemiological classes, susceptible (S), Exposed (E), infected (I). These classes are further

interact with each other, different susceptibilities, and infectiousness based on the seasonality of the infection and immunity and control. We take into account the differences in infectivity for diseases such as the Influenza, i.e., latent or incubation period (E), and symptomatic or infectious period (I). We apply the model to the case of Morocco, and assume that the course of the outbreak is short compared with the life of an individual, therefore, births, and natural deaths are equal.

In the SEIS model, it is assumed that the population consists of susceptible (S), exposed (E), infected and infectious (I) individuals. A characteristic feature of the seasonal Influenza is that immunity after infection is temporary, so that the infected individuals become susceptible again. The model depends on several parameters: The parameter μ, which denotes the birth rate, assumed equal to the mortality rate; and α, which is the rate of loss of infectiousness, thus, an infected individuals become susceptible again at a rate αI. The parameter γ denotes the average incubation period, thus , exposed individuals become infectious at a rate γE. Since health authorities and institutions usually interfere in such a situation of pandemics and epidemics to save lives, we thus incorporate the control intervention into the model as a parameter u, thus the treated individuals become susceptible at a rate uI.

The disease transmission is modeled using the standard incidence, given by

$$\frac{\beta IS}{N}$$

Then, the SEIS model for The Influenza epidemic is given by the following system of ordinary differential equations:

$$\frac{dS}{dt} = \mu N - \frac{\beta IS}{N} - \mu S + \alpha I + uI \tag{1}$$

$$\frac{dE}{dt} = \frac{\beta IS}{N} - \mu E - \gamma E \tag{2}$$

$$\frac{dI}{dt} = \gamma E - (\mu + \alpha + u) I \tag{3}$$

Where $S(0) \geq 0$, $I(0) \geq 0$ and $E(0) \geq 0$, and $N = S + E + I$. Moreover, the influence of the seasonality on the transmission and control parameters is modeled by the cosine and sine

functions and given by

$$\beta(t) = b_0\left(1 + b_1 \sin\left(\frac{2\pi b_2 t}{7200} - \frac{b_3\pi}{200}\right)\right)$$

$$\gamma(t) = a_0\left(1 + a_1 \sin\left(\frac{2\pi a_2 t}{7200} - \frac{a_3\pi}{200}\right)\right)$$

$$u = \cos\left(\frac{2\pi c}{365}\right)$$

Note that b_0 and a_0 are the averages of the transmission parameters, b_1 and a_1 are the amplitudes of the seasonal fluctuation in the transmission parameters β and γ, respectively, while b_2, b_3, a_2 and a_3 are angle parameters that will be chosen later in agreement with the real data for $I(t)$.

3. Stability Analysis

In this section, we find the basic reproduction number and stability of the model. We prove that our model is locally and stable for both disease-free-equilibrium and endemic equilibrium points.

To work in term of proportions we take $s = \frac{S}{N}$, $e = \frac{E}{N}$ and $i = \frac{I}{N}$, then we have the following reduced system

$$\frac{ds}{dt} = \mu - \beta si - \mu s + \alpha i + ui \tag{4}$$

$$\frac{de}{dt} = \beta si - \mu e - \gamma e \tag{5}$$

$$\frac{di}{dt} = \gamma e - (\mu + \alpha + u)\, i \tag{6}$$

This system has two equilibria, the disease-free equilibrium $e_0 = (1,0,0)$ and the endemic equilibrium

$$e^* = \left(\frac{\gamma+\mu}{\beta}, -\frac{(\alpha+\mu+u)\,(\gamma-\beta+\mu)}{\beta\,(\alpha+\gamma+\mu+u)}, -\frac{\gamma\,(\gamma-\beta+\mu)}{\beta\,(\alpha+\gamma+\mu+u)}\right)$$

In epidemiology, the basic reproduction number R_0 is the average number of secondary infectious cases produced by a single infection in total susceptible population. Based on the

next-generation matrix method [4] we compute the basic reproductive number R_0, which is given by

$$R_0 = \frac{\beta}{\gamma+\mu}$$

Note that also the basic reproductive number R_0 is a function of time, since the parameters β and γ are seasonal parameters.

Proposition 1. *The disease-free equilibrium e_0 is stable if $R_0 < 1$, otherwise it is unstable.*

Proof. By computing the Jacobian matrix associated with the system (4)-(6) at the disease-free equilibrium, we have

$$J(e_0) = \begin{pmatrix} -\mu & -\beta & \alpha+u \\ 0 & \beta-\gamma-\mu & 0 \\ 0 & \gamma & -\alpha-\mu-u \end{pmatrix}$$

Its eigenvalues are

$$-\mu$$
$$\beta-\gamma-\mu$$
$$-\alpha-\mu-u$$

It is clear that the eigenvalues of $J(e_0)$ are negatives if and only if $\beta-\gamma-\mu < 0$ which means, if and only if $R_0 < 1$, which completes the proof. □

Proposition 2. *The endemic equilibrium e^* is locally asymptotically stable if $R_0 > 1$.*

Proof. By computing the Jacobian matrix associated with the system (4)-(6) at the endemic equilibrium, we have

$$J(e^*) = \begin{pmatrix} -\frac{\alpha\beta-\alpha\gamma+\beta\mu+\beta u-\gamma u}{\alpha+\gamma+\mu+u} & -\gamma-\mu & \alpha+u \\ -\frac{(\alpha+\mu+u)(\gamma-\beta+\mu)}{\alpha+\gamma+\mu+u} & 0 & 0 \\ 0 & \gamma & -\alpha-\mu-u \end{pmatrix}$$

Where the characteristic polynomial of $J(e^*)$ is

$$\lambda^3 + c_1\lambda^2 + c_2\lambda + c_3$$

Where

$$c_1 = \frac{\alpha\beta + 2\alpha\mu + \beta\mu + \gamma\mu + 2\alpha u + \beta u + 2\mu u + \alpha^2 + \mu^2 + u^2}{\alpha + \gamma + \mu + u}$$

$$c_2 = -\frac{(\alpha + \mu + u)\left(\alpha\gamma - \alpha\beta - \beta\gamma - 2\beta\mu + 2\gamma\mu - \beta u + \gamma u + \gamma^2 + \mu^2\right)}{\alpha + \gamma + \mu + u}$$

$$c_3 = -\mu\,(\alpha + \mu + u)\,(\gamma - \beta + \mu)$$

It is clear that $c_1 > 0$. The fact $R_0 > 1$ implies that $\gamma - \beta + \mu < 0$, which means that $c_3 > 0$.

Let $c_2 = -\frac{(\alpha+\mu+u)U}{\alpha+\gamma+\mu+u}$

where

$$U = \alpha\gamma - \alpha\beta - \beta\gamma - 2\beta\mu + 2\gamma\mu - \beta u + \gamma u + \gamma^2 + \mu^2$$

Let

$$V = (\gamma - \beta + \mu)\,(\alpha + \gamma + \mu + u)$$

and

$$W = \alpha\mu + \beta\mu + \mu u$$

One can easily verify that

$$U = V - W$$

It is clear that $W > 0$ and by $R_0 > 1$ we get also $V < 0$, thus $U < 0$, and then $c_2 > 0$. Using the Routh-Hurwitz stability criterion, we conclude that the equilibrium point e^* is locally asymptotically stable. □

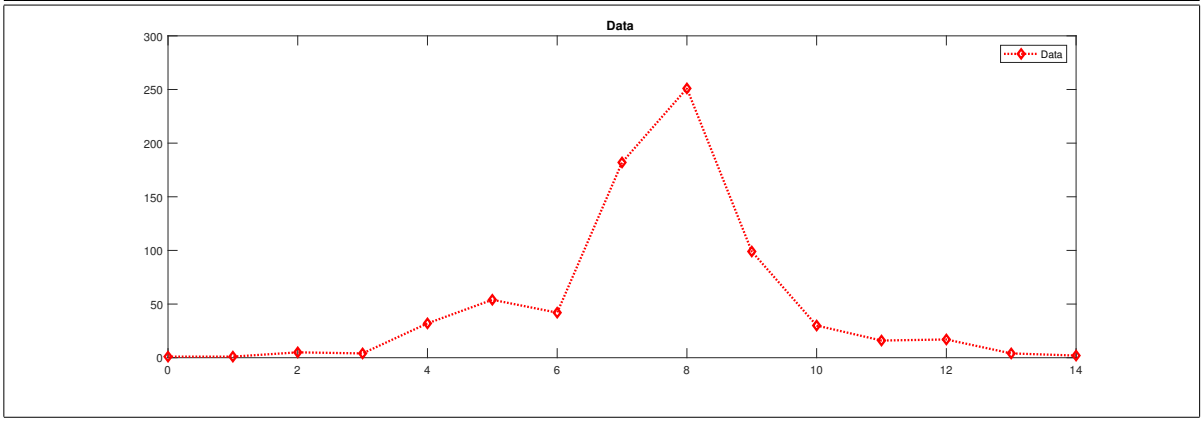
4. PARAMETERS ESTIMATION

To verify the reality of the model we propose here, we use nonlinear least-squares regression to fit the model to actual observations for the situation of the Influenza A epidemic in Morocco given [28] from 2018-12-10 to 2019-03-24 and presented in Table 1. Therefore, the following process has been followed for parameters estimation:

In this section we present the process of the parameters' estimation [29]. Using MATLAB ode45 routine, the system of ordinary differential equations is solved numerically, with initial chosen values for parameters and state variables. Model outcomes are compared with the field data and the Levenberg–Marquardt optimization algorithm determines a new set of parameters

TABLE 1. Data of the influenza epidemic in morocco from 2018-12-10 to 2019-03-24 [28]

From	To	Number of infected individuals
2018-12-10	2018-12-16	1
2018-12-17	2018-12-23	1
2018-12-24	2018-12-30	5
2018-12-31	2019-01-06	4
2019-01-07	2019-01-13	32
2019-01-14	2019-01-20	54
2019-01-21	2019-01-27	42
2019-01-28	2019-02-03	182
2019-02-04	2019-02-10	251
2019-02-11	2019-02-17	99
2019-02-18	2019-02-24	30
2019-02-25	2019-03-03	16
2019-03-04	2019-03-10	17
2019-03-11	2019-03-17	4
2019-03-18	2019-03-24	2



values with the model outcomes in a better fit to the field data [30, 31]. After new parameters values are determined by this optimizer, the system of ordinary differential equations is solved numerically using these new parameters value and the model outcomes are compared again with the field data. This iteration process between parameter updating and numerical solutions of the system of ordinary differential equations using Runge–Kutta method [32, 33] continue till convergence criteria for the parameters are met. In this process of estimating parameters,

TABLE 2. Estimated parameters values

b_0	b_1	b_2	α	μ	a_0	c	b_3	a_1	a_2	a_3
6.3290	0.9991	579.4704	0.9000	0.0200	0.8049	0.0073	388.2570	0.9601	709.2605	225.8000

about one thousand values are chosen using a random process for each of the parameters to be estimated. Estimated parameters values for Model (1)-(3) are given in Table 2. Fig. 1 depicts the effectiveness of the parameters' estimation, where we can see that the SEIS model we propose here fits correctly the real data.

Fig.2 depicts the validity of the estimated parameters, where in the left sub-figure we can see the different values of the residuals of the estimation of parameters, and in the right sub-figure we check the normality of residuals. This means that the estimated parameters are reliable and the model that we propose here is valid.

Based on the estimated parameters given the Table 2, we simulate the seasonal basic reproductive number R_0 in the Fig.3. Where we can see that R_0 rise continuously to exceed 240 by about four weeks, and then it starts to decrease towards 0 by the 7th week. It can be seen from that figure that this first wave of R_0 is followed by an increasing of the infections, which can be interpreted by the incubation period of the Influenza epidemic. When R_0 exceeds 1, the infections will increase after a while by approximately 3 weeks. Again we can see in this figure that R_0 starts to increase up to 200 and then decrease. This means that a second wave of infection is possible. Notwithstanding this rise in the basic reproductive number, it is fortunate that Morocco did not record any second wave.

5. SENSITIVITY ANALYSIS

Sensitivity analysis is measured using the sensitivity index. Sensitivity indices allow us to measure the relative change in a state variable when a parameter changes while the other parameters are retained fixed at constant values. The normalized forward sensitivity index of a variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. When the variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives.

FIGURE 1. Comparison of the number of infective individuals registered in Morocco [28] with the ones predicted by the SEIS model (1)-(3) with the estimated parameter values given in Table 2.

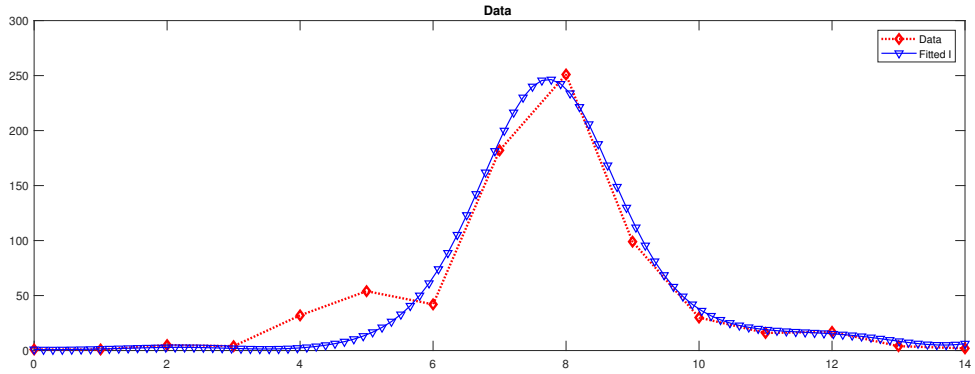


FIGURE 2. Residuals of the estimation of the parameters. Left: Residuals. Right: Normality of residuals.

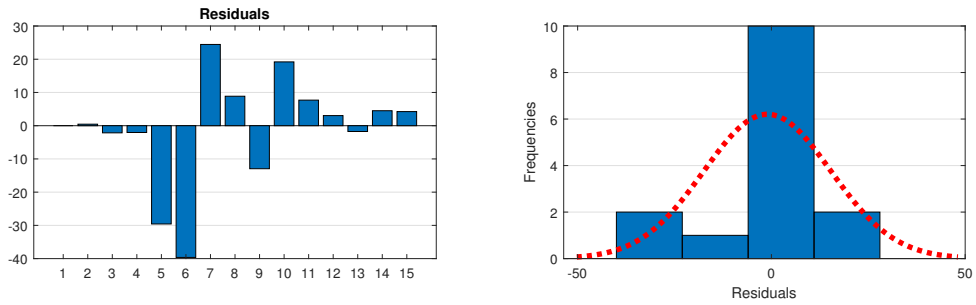
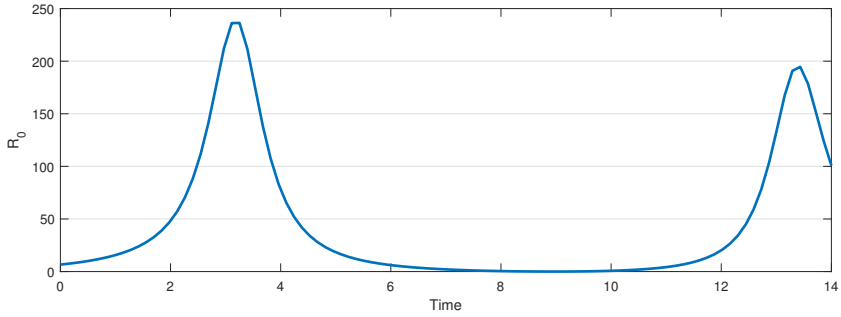


FIGURE 3. The seasonal basic reproductive number R_0 as a function of time.



We carried out local sensitivity indices of R_0 to the model parameters. A sensitivity index of 1 indicates that a variation of 10% of the parameter causes a variation of 10% of the final value of R_0. Indices less than 0 show a negative fluctuation, while those greater than 0 show a positive variation.

At a fixed instant t, the threshold R_0 is a function of eight parameters b_0, b_1, b_2, b_3, a_0, a_1, a_2, a_3, and μ where

$$R_0 = \frac{\beta}{\gamma+\mu} = \frac{b_0\left(1+b_1\sin\left(\frac{2\pi b_2 t}{7200}-\frac{b_3\pi}{200}\right)\right)}{a_0\left(1+a_1\sin\left(\frac{2\pi a_2 t}{7200}-\frac{a_3\pi}{200}\right)\right)+\mu}$$

A small perturbation δ_x to a parameter x and the corresponding change in R_0 as δR_0 is given by

$$\begin{aligned}\delta R_0 &= R_0(x+\delta_x) - R_0(x)\\ &= \frac{R_0(x+\delta_x)-R_0(x)}{\delta_x}\delta_x\\ &\cong \delta_x\frac{\partial R_0}{\partial x}\end{aligned}$$

Thus, the normalized sensitivity index ϕ_x is defined as

$$\phi_x = \frac{\partial R_0}{R_0}\Big/\frac{\partial x}{x} = \frac{x}{R_0}.\frac{\partial R_0}{\partial x}$$

Therefore normalized sensitivity indices for the 8 parameters are obtained as

$$\begin{aligned}\phi_{b_0} &= 1\\ \phi_{b_1} &= \frac{b_1\sin\left(\frac{\pi(18b_3-b_2t)}{3600}\right)}{b_1\sin\left(\frac{\pi(18b_3-b_2t)}{3600}\right)-1}\\ \phi_{b_2} &= -\frac{\pi b_1 b_2 t\cos\left(\frac{\pi(18b_3-b_2t)}{3600}\right)}{3600\left(b_1\sin\left(\frac{\pi(18b_3-b_2t)}{3600}\right)-1\right)}\\ \phi_{b_3} &= \frac{\pi b_1 b_3\cos\left(\frac{\pi(18b_3-b_2t)}{3600}\right)}{200\left(b_1\sin\left(\frac{\pi(18b_3-b_2t)}{3600}\right)-1\right)}\\ \phi_{a_0} &= \frac{a_0\left(a_1\sin\left(\frac{\pi(18a_3-a_2t)}{3600}\right)-1\right)}{a_0+\mu-a_0a_1\sin\left(\frac{\pi(18a_3-a_2t)}{3600}\right)}\\ \phi_{a_1} &= \frac{a_0a_1\sin\left(\frac{\pi(18a_3-a_2t)}{3600}\right)}{a_0+\mu-a_0a_1\sin\left(\frac{\pi(18a_3-a_2t)}{3600}\right)}\end{aligned}$$

$$\phi_{a_2} = -\frac{\pi a_0 a_1 a_2 t \cos\left(\frac{\pi(18a_3 - a_2 t)}{3600}\right)}{3600\left(a_0 + \mu - a_0 a_1 \sin\left(\frac{\pi(18a_3 - a_2 t)}{3600}\right)\right)}$$

$$\phi_{a_3} = \frac{\pi a_0 a_1 a_3 \cos\left(\frac{\pi(18a_3 - a_2 t)}{3600}\right)}{200\left(a_0 + \mu - a_0 a_1 \sin\left(\frac{\pi(18a_3 - a_2 t)}{3600}\right)\right)}$$

$$\phi_{\mu} = -\frac{\mu}{a_0 + \mu - a_0 a_1 \sin\left(\frac{\pi(18a_3 - a_2 t)}{3600}\right)}$$

If $\phi_x = 0.01$, thus, increasing (or decreasing) x by 10% increases (or decreases) R_0 by 0.1%. For instance, since $\phi_{b_0} = 1$, thus, decreasing (or increasing) b_0 by 10% decreases (or increases) R_0 by 10%. Sensitivity indices for seasonal parameters b_1, b_2, b_3, a_0, a_1, a_2, a_3 and μ are depicted in Fig.4 and Fig.5.

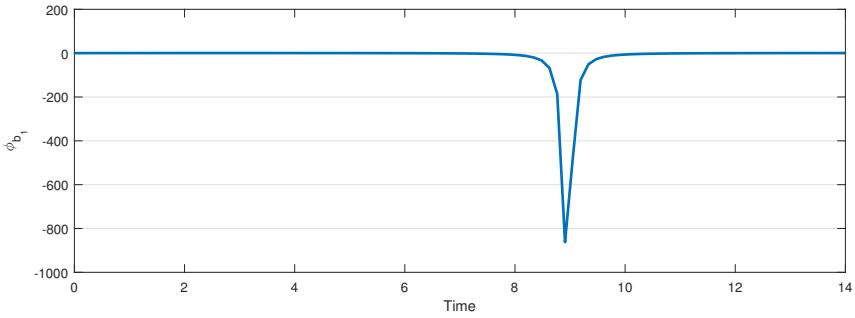
6. Model Uncertainty

A covariance matrix estimates variability of the model parameters and hence random disturbances in the output. Thus covariance matrices contain information about the uncertainties in model output. All covariance matrices are symmetrical. The absolute value giving accuracy information is contained in the diagonal elements of covariance matrix. All other elements in covariance matrices can be used to study the inter-relationships. If the covariance between any two coefficients is positive, then the coefficients values tend to vary in a positive way. On the other hand, if the covariance between any two coefficients is negative, then the coefficients values tend to move in opposite directions. Also, covariance matrix provides uncertainties on the parameters estimation that captures relations in the measurement uncertainties. The following matrix $\sum$ represents the covariance matrix for the SIS model (1)-(3) with the Influenza epidemic data.

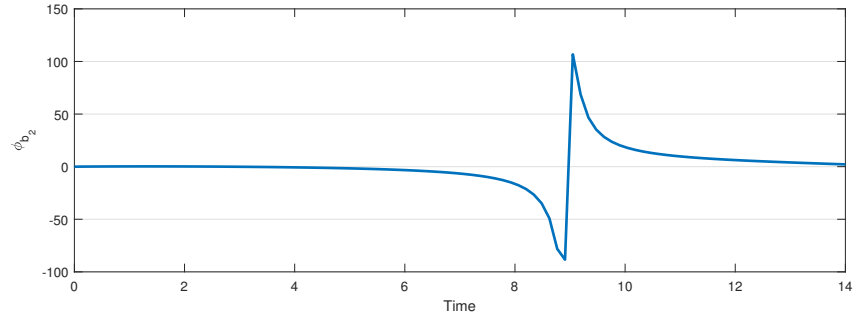
$$\Sigma = \begin{pmatrix}
 & b_1 & \alpha & \mu & b_0 & b_2 & a_0 & c & b_3 & a_1 & a_2 & a_3 \\
b_1 & 32.91892692 & -292.5837047 & -15.08406254 & 121.1848362 & -657.7578808 & -110.2557322 & -62441829.61 & -2184.745992 & 9.678075924 & 1598.256547 & -549.469777 \\
\alpha & -292.5837047 & 6633.365446 & -576.9665502 & 5007.38661 & -27754.77938 & 332.095068 & 774969222.3 & 3225.039213 & -155.1540823 & -10268.93009 & 26832.33515 \\
\mu & -15.08406254 & -576.9665502 & 165.31921 & -824.0192106 & 3401.740605 & 142.5170879 & -2605277.311 & 2351.197787 & 4.899621654 & -3476.409762 & -5120.483078 \\
b_0 & 121.1848362 & 5007.38661 & -824.0192106 & 12696.75039 & -82272.9447 & -1613.131627 & 142290177.2 & -47878.86104 & -96.79270756 & -8466.06034 & 16972.64475 \\
b_2 & -657.7578808 & -27754.77938 & 3401.740605 & -82272.9447 & 603787.0139 & 9773.493432 & -926675088.8 & 339362.8778 & 632.6632044 & 168124.9463 & -19474.48129 \\
a_0 & -110.2557322 & 332.095068 & 142.5170879 & -1613.131627 & 9773.493432 & 490.7760545 & 171495980.4 & 11067.65766 & -19.20291607 & -4567.238846 & -695.7726308 \\
c & -62441829.61 & 774969222.3 & -2605277.311 & 142290177.2 & -926675088.8 & 171495980.4 & 1.3569195\,10^{14} & 3061640840.0 & -22438312.45 & -3216903050.0 & 1856155140.0 \\
b_3 & -2184.745992 & 3225.039213 & 2351.197787 & -47878.86104 & 339362.8778 & 11067.65766 & 3061640840.0 & 293849.2148 & -236.0941501 & -4196.665356 & 26749.69035 \\
a_1 & 9.678075924 & -155.1540823 & 4.899621654 & -96.79270756 & 632.6632044 & -19.20291607 & -22438312.45 & -236.0941501 & 4.428921428 & 605.2780479 & -400.2002854 \\
a_2 & 1598.256547 & -10268.93009 & -3476.409762 & -8466.06034 & 168124.9463 & -4567.238846 & -3216903050.0 & -4196.665356 & 605.2780479 & 347648.0746 & 166517.8713 \\
a_3 & -549.469777 & 26832.33515 & -5120.483078 & 16972.64475 & -19474.48129 & -695.7726308 & 1856155140.0 & 26749.69035 & -400.2002854 & 166517.8713 & 248357.8034
\end{pmatrix}$$

FIGURE 4. Sensitivity indices for the seasonal parameters b_1 , b_2, b_3 and μ.(a) $\phi_{b_1}(t)$. (b) $\phi_{b_2}(t)$. (c) $\phi_{b_3}(t)$. (d) $\phi_{\mu}(t)$.

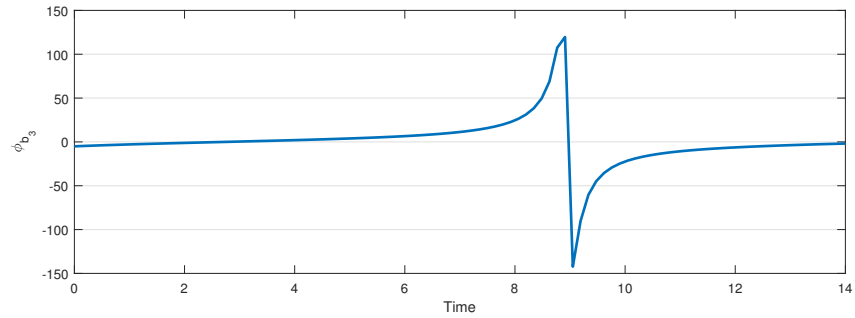
(a)



(b)



(c)



(d)

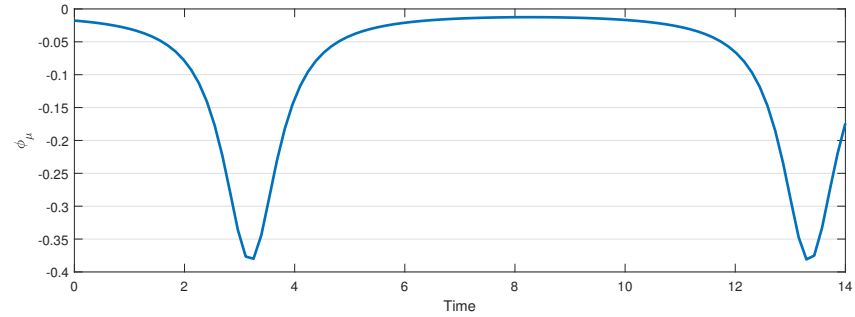
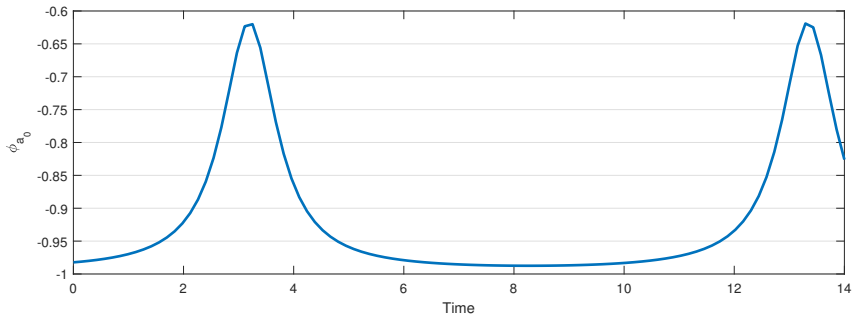
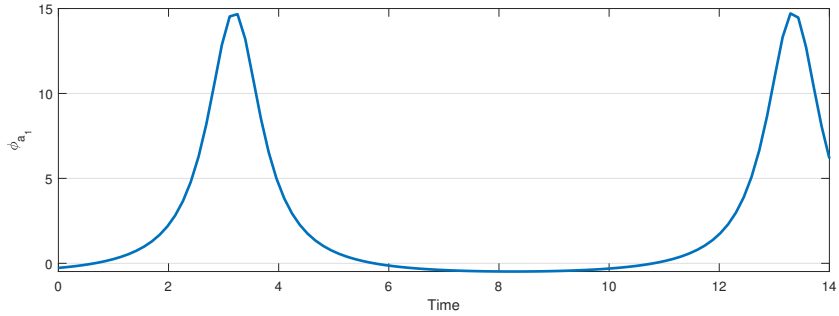


FIGURE 5. Sensitivity indices for the seasonal parameters a_0, a_1, a_2 and a_3.(a) $\phi_{a_0}(t)$. (b) $\phi_{a_1}(t)$. (c) $\phi_{a_2}(t)$. (d) $\phi_{a_3}(t)$.

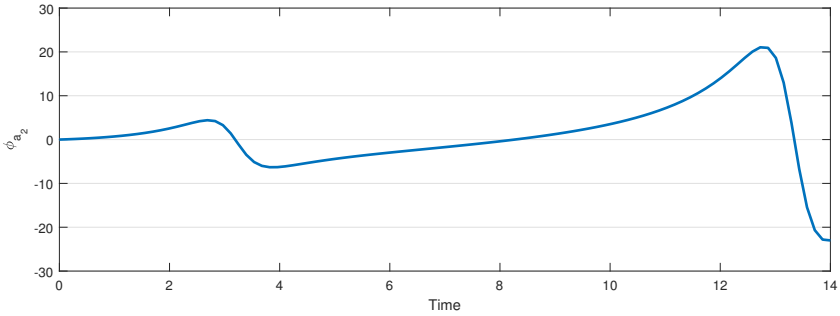
(a)



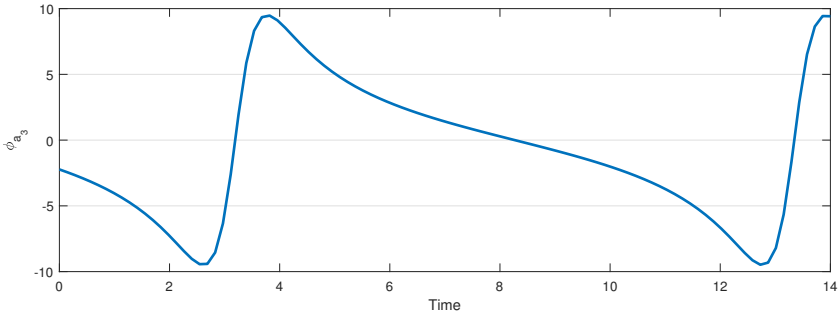
(b)



(c)



(b)



The variance of each parameters is shown in the leading diagonal elements of the covariance matrix $\sum$. The parameter c has the largest variance ($1.3569195\,10^{14}$) followed by the parameter b_2 (603787.0139), the parameter a_2 (347648.0746), the parameter b_3 (293849.2148), the parameter a_3 (248357.8034), the parameter b_0 (12696.75039), the parameter α (6633.365446), the parameter a_0 (490.7760545), the parameter μ (165.31921), the parameter b_1 (32.91892692), and the parameter a_1 (4.428921428).

The covariance matrix $\sum$ contains negative and positive elements, negative covariance means that the parameters values on those parameters tend to move in opposite directions which means that if one parameter's value increases then other parameter's value start decreasing. While positive covariances mean that these parameters values tend to vary in a positive way which means that if one parameter's value increases then other parameter's value also increases.

As shown in the covariance matrix $\sum$, the covariance between the coefficients b_1 and α is negative (-292.5837047), the covariance between the coefficients b_1 and μ is negative (-15.08406254), the covariance between the coefficients b_1 and b_2 is negative (-657.7578808), the covariance between the coefficients b_1 and a_0 is negative (-110.2557322), the covariance between the coefficients b_1 and c is negative (-62441829.61), the covariance between the coefficients b_1 and b_3 is negative (-2184.745992), the covariance between the coefficients b_1 and a_3 is negative (-549.469777).

The covariance between the coefficients α and μ is negative (-576.9665502), the covariance between the coefficients α and b_2 is negative (-27754.77938), the covariance between the coefficients α and a_1 is negative (-155.1540823), the covariance between the coefficients α and a_2 is negative (-10268.93009). The covariance between the coefficients μ and b_0 is negative (-824.0192106), the covariance between the coefficients μ and c is negative (-2605277.311), the covariance between the coefficients μ and a_2 is negative (-3476.409762), the covariance between the coefficients μ and a_3 is negative (-5120.483078). The covariance between the coefficients b_0 and b_2 is negative (-82272.9447), the covariance between the coefficients b_0 and a_0 is negative (-1613.131627), the covariance between the coefficients b_0 and b_3 is negative (-47878.86104), the covariance between the coefficients b_0 and a_1 is negative (-96.79270756), the covariance between the coefficients b_0 and a_2 is negative (-8466.06034). The covariance

between the coefficients b_2 and c is negative (-926675088.8), the covariance between the coefficients b_2 and a_3 is negative (-19474.48129). The covariance between the coefficients a_0 and a_1 is negative (-19.20291607), the covariance between the coefficients a_0 and a_2 is negative (-4567.238846), the covariance between the coefficients a_0 and a_3 is negative (-695.7726308). The covariance between the coefficients c and a_1 is negative (-22438312.45), the covariance between the coefficients c and a_2 is negative (-3216903050.0). The covariance between the coefficients b_3 and a_1 is negative (-236.0941501), the covariance between the coefficients b_3 and a_2 is negative (-4196.665356). The covariance between the coefficients a_1 and a_3 is negative (-400.2002854). This reflect that these parameters values tend to vary in a negative way.

The covariance between the coefficients b_1 and the b_0 is positive (121.1848362), the covariance between the coefficients b_1 and the a_1 is positive (9.678075924), the covariance between the coefficients b_1 and the a_2 is positive (1598.256547). The covariance between the coefficients α and the b_0 is positive (5007.38661), the covariance between the coefficients α and the a_0 is positive (332.095068), the covariance between the coefficients α and the c is positive (774969222.3), the covariance between the coefficients α and the b_3 is positive (3225.039213), the covariance between the coefficients α and the a_3 is positive (26832.33515). The covariance between the coefficients μ and the b_2 is positive (3401.740605), the covariance between the coefficients μ and the a_0 is positive (142.5170879), the covariance between the coefficients μ and the b_3 is positive (2351.197787), the covariance between the coefficients μ and the a_1 is positive (4.899621654). The covariance between the coefficients b_0 and the c is positive (142290177.2), the covariance between the coefficients b_0 and the a_3 is positive (16972.64475). The covariance between the coefficients b_2 and the a_0 is positive (9773.493432), the covariance between the coefficients b_2 and the b_3 is positive (339362.8778), the covariance between the coefficients b_2 and the a_1 is positive (632.6632044), the covariance between the coefficients b_2 and the a_2 is positive (168124.9463). The covariance between the coefficients a_0 and the c is positive (171495980.4), the covariance between the coefficients a_0 and the b_3 is positive (11067.65766). The covariance between the coefficients c and the b_3 is positive (3061640840.0), the covariance between the coefficients c and the a_3 is positive (1856155140.0). The covariance

TABLE 3. Summary of covariance.

Covariance	Direction	Covariance	Direction	Covariance	Direction	Covariance	Direction	Covariance	Direction
$C_{b_1,\alpha}$	$-ve$	C_{α,b_0}	$+ve$	$C_{\mu,c}$	$-ve$	C_{b_0,a_3}	$+ve$	C_{a_0,a_3}	$-ve$
$C_{b_1,\mu}$	$-ve$	C_{μ,b_2}	$-ve$	C_{μ,b_3}	$+ve$	C_{b_2,a_0}	$+ve$	C_{c,b_3}	$+ve$
C_{b_1,b_0}	$+ve$	C_{μ,a_0}	$+ve$	C_{μ,a_1}	$+ve$	$C_{b_2,c}$	$-ve$	C_{c,a_1}	$-ve$
C_{b_1,b_2}	$-ve$	$C_{\mu,c}$	$+ve$	C_{μ,a_2}	$-ve$	C_{b_2,b_3}	$+ve$	C_{c,a_2}	$-ve$
C_{b_1,a_0}	$-ve$	C_{μ,b_3}	$+ve$	C_{μ,a_3}	$-ve$	C_{b_2,a_1}	$+ve$	C_{c,a_3}	$+ve$
$C_{b_1,c}$	$-ve$	C_{μ,a_1}	$-ve$	C_{b_0,b_2}	$-ve$	C_{b_2,a_2}	$+ve$	C_{b_3,a_1}	$-ve$
C_{b_1,b_3}	$-ve$	$C_{\mu,2_2}$	$-ve$	C_{b_0,a_0}	$-ve$	C_{b_2,a_3}	$-ve$	C_{b_3,a_2}	$+ve$
C_{b_1,a_1}	$+ve$	C_{μ,a_3}	$+ve$	$C_{b_0,c}$	$+ve$	$C_{a_0,c}$	$+ve$	C_{b_3,a_3}	$-ve$
C_{b_1,a_2}	$+ve$	C_{μ,b_0}	$-ve$	C_{b_0,b_3}	$-ve$	C_{a_0,b_3}	$+ve$	C_{a_1,a_2}	$+ve$
C_{b_1,a_3}	$-ve$	C_{μ,b_2}	$+ve$	C_{b_0,a_1}	$-ve$	C_{a_0,a_1}	$-ve$	C_{a_1,a_3}	$-ve$
$C_{\alpha,\mu}$	$-ve$	C_{μ,a_0}	$+ve$	C_{b_0,a_2}	$-ve$	C_{a_0,a_2}	$-ve$	C_{a_2,a_3}	$+ve$

between the coefficients c and the a_3 is positive (26749.69035). The covariance between the coefficients a_1 and the a_2 is positive (605.2780479). The covariance between the coefficients a_2 and the a_3 is positive (166517.8713). This means that these parameters values vary in a positive way.

Table 3 shows the summary of covariance of the Influenza epidemic model parameters.

7. CONCLUSION

In this paper, a SEIS model type compartmental model has been considered to explore the evolution of the Influenza epidemic in Morocco. To consider a more realistic model we consider the seasonality of parameters, by considering time-dependent infection rate, time-dependent recovery rate, and time-dependent intervention rate. The next-generation matrix method is used to compute the threshold of equilibria's stability R_0. A real data of Influenza epidemic A infections in Morocco from the Influenza Laboratory Surveillance Information system is used to estimate the model parameters. In order to identify the most influential parameter in the proposed model, sensitivity analysis is carried out. We calculated sensitivity indices based on the estimated parameters to identify the most influential parameters. We found that the seasonal parameters a_0, a_1, a_2, and a_3 are most influential in the first four weeks and the last two weeks. While the parameters b_1, b_2, and b_3 are the most influential parameters of the eighth and ninth weeks. Finally, the moderate influence of the μ parameter during the first and last

weeks. Uncertainty analysis is carried out to determine the relationship between the different parameters of the model.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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