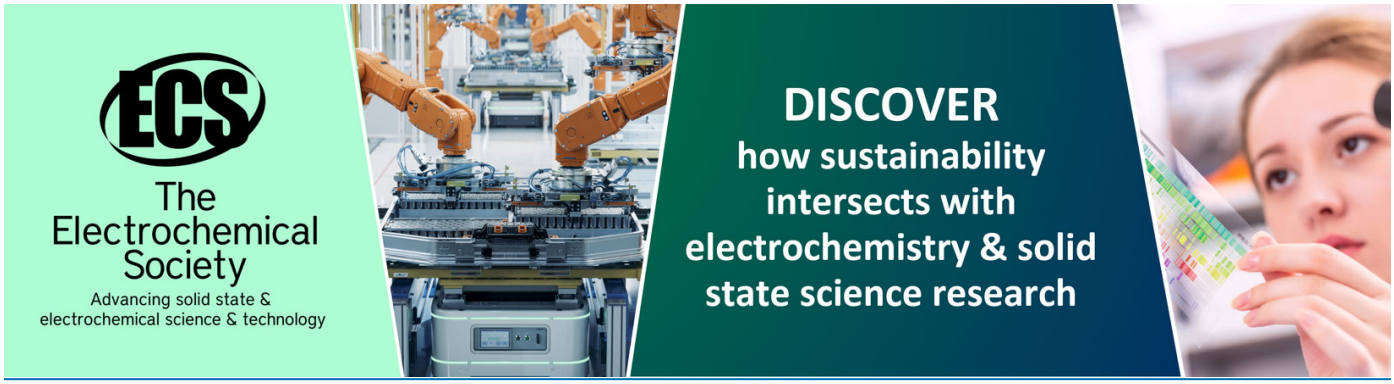
Some Preliminary Results on an SEIARD Epidemic Model with Vaccination and Antiviral Treatment Controls and Dead-Infective Culling Action



Some Preliminary Results on an SEIARD Epidemic Model with Vaccination and Antiviral Treatment Controls and Dead-Infective Culling Action

M. De la Sen[1], **R. Nistal, S. Alonso-Quesada, A. J. Garrido**
Institute of Research and Development of Processes,
University of the Basque Country,
Bilbao, Spain

E-mail: manuel.delasen@ehu.es

Abstract. This paper studies the non-negativity and stability properties of the solutions of a newly proposed SEIADR model which incorporates asymptomatic and dead-infective subpopulations to those defining the standard SEIR model and, in parallel, it incorporates feedback vaccination and antiviral treatment controls.

1. Introduction

Relevant attention is being paid in the last two decades to the study of mathematical epidemic models, which are modelled by integro-differential equations and/ or difference equations. Those models describe the evolution of the various subpopulations considered as the disease under study progresses. Typically, the models have three essential subpopulations (namely, susceptible, infected and recovered by immunity) whose dynamics are mutually coupled. There are different degrees of complexity available in the statement of the models. The simpler models basically describe "susceptible" (S) and "infected" (I) subpopulations and are referred to as SI- models. A second degree of complexity adds a third one said to be the "recovered by immunity" subpopulation and those models are said to be SIR-models. A further complexity degree splits the infected into two subpopulations (or compartments), namely, the so-called "infected" or "exposed" (E) (those infective having the disease but do not present yet external symptoms) and the "infectious" or "infective" (those infective having external symptoms). The generic acronym used for this last category of models is SEIR, being referred to as SEIR epidemic models. A general description of epidemic models and some mathematical analysis on them is given in some classical books. See, for instance, [1-2]. More sophisticated models have been described and analyzed in the literature. See, for instance, [4-8] and references therein. On the other hand, it turns out, due to medical experience, that there are individuals who are infected but do not have significant external symptoms, the so-called the "asymptomatic" (A) subpopulation. This occurs even in the common known influenza disease. If such an asymptomatic subpopulation is considered in the model then it turns out that the exposed have potential distinct transitions to the infective and to the asymptomatic so that a part of the exposed become asymptomatic after some time while others become infective. On the other hand, it is well-known that in the Ebola disease case, the abandoned

[1] To whom any correspondence should be addressed. This research is supported by the Spanish Government through Grants DPI2012-30651 and DPI2015-64766-R

lying dead corpses are infective [3, 4] what causes serious sanitary problems in third world tropical countries with low or scarce sanitary technical means when Ebola disease spreads thoroughly specially when it is transmitted from scarcely populated rural areas to high populated urban ones. In particular, it has been pointed out in some background literature that the simultaneous presence of asymptomatic infective population with dead-infective corpses is compatible in the Ebola disease propagation. The dead lying corpses can be considered in the model as a new infective subpopulation "D".

2. The model and its controlling actions

The proposed SEIADR model is the following:

$$\dot{S}(t) = b_1 - (b_2 + \beta I(t) + \beta_A A(t) + \beta_D D(t))S(t) + \eta R(t) - V(t)$$
$$\dot{E}(t) = -(b_2 + \gamma)E(t) + (\beta I(t) + \beta_A A(t) + \beta_D D(t))S(t)$$
$$\dot{I}(t) = -(b_2 + \alpha + \tau_0 + \xi(t))I(t) + \gamma p E(t)$$
$$\dot{A}(t) = -(b_2 + \tau_0)A(t) + \gamma(1-p)E(t)$$
$$\dot{D}(t) = -\mu D(t) + b_2(I(t) + A(t)) + \alpha I(t) - \rho_D(t)D(t)\Sigma_{t_i \in ImpD}\delta(t - t_i)$$
$$\dot{R}(t) = -(b_2 + \eta)R(t) + \tau_0(I(t) + A(t)) + \xi(t)I(t) + V(t)$$

; $\forall t \in \boldsymbol{R}_{0+}$ with initial conditions satisfying $min(S(0), E(0), I(0), A(0), D(0), R(0)) \geq 0$, where:

$\delta(t)$ is the Dirac distribution, $ImpD = \{t \in \boldsymbol{R}_{0+} : D(t) \neq D(t^-)\} = \cup_{t \in \boldsymbol{R}_{0+}} ImpD(t)$, with $\boldsymbol{R}_{0+} = \boldsymbol{R}_+ \cup \{0\} = \{t \in \boldsymbol{R} : t \geq 0\}$, is the total set of impulsive ("culling") time instants where actions or removal of infective corpses are performed, (the notation for $f(t^+)$ is simplified to $f(t)$), and

$ImpD(t^-) = \{\sigma \in ImpD : \sigma < t\}$,

$ImpD(t) = \{\sigma \in ImpD : \sigma \leq t\} = ImpD(t^-)$ if $t \notin ImpD$, and

$ImpD(t) = \{\sigma \in ImpD : \sigma \leq t\} = ImpD(t^-) \cup \{t\}$ if $t \in ImpD$

and the (nonnegative) parameters and controls are the following:

b_1 is the recruitment rate,

b_2 is the natural average death rate,

β, β_A, β_D are the various disease transmission coefficients to the susceptible from the respective infective, asymptomatic and infective corpses subpopulations,

η is a parameter such that $1/\eta$ is the average duration of the immunity period reflecting a transition from the recovered to the susceptible,

γ is the transition rate from the exposed to all (i.e. both symptomatic and asymptomatic) infectious,

α is the average extra mortality associated with the symptomatic infectious subpopulation,

τ_0 is the natural immune response rate for the whole infectious subpopulation (i.e. $A + I$), respectively,

p is the fraction of the exposed, which become standard infectious,

$1 - p$ is the fraction of the exposed which become asymptomatic infectious,

$1/\mu$ is the average period of infectiousness after death,

$V(t)$ and $\xi(t)$ are, respectively, the vaccination and antiviral treatment controls and $\rho_D(t_i)D(t_i)$ is the impulsive action of removal of corpses (or "culling") for all $t_i \in ImpD$ with $\rho_D(t) \in [0,1]$, $\rho_D(t) \in (0,1]$ if $t \in ImpD$, being the fraction of corpses removal. The controls can be of different types including constant and feedback actions.

The proposed time-varying feedback vaccination and antiviral treatment laws, eventually including feedback impulses on the susceptible and symptomatic infective subpopulations, are the following:

$V(t) = V_0 + K_V(t)S(t) + \rho_V(t)S(t)\sum_{t_i \in ImpS} \delta(t - t_i)$

$\xi(t) = \xi_0 + K_\xi(t)I(t) + \rho_\xi(t)I(t)\sum_{t_i \in Imp\,I} \delta(t - t_i)$

; $\forall t \in \boldsymbol{R}_{0+}$, where $V_0 \geq 0$, $\xi_0 \geq 0$, K_V, $K_\xi \in PC^0(\boldsymbol{R}_{0+}, [0,1])$ and *ImpS* and *Imp I* are the sets of impulsive time instants for the vaccination action on the susceptible and antiviral action on the symptomatic infective, $\rho_V(t) \in [0,1]$ and $\rho_\xi(t) \in [0,1]$; $\forall t \in \boldsymbol{R}_{0+}$ give the fractions of vaccinated susceptible or antiviral infective treated subpopulations.

3. Some model properties

The proposed SEIADR model has the following properties which have been rigorously proved but the proofs are omitted by space reasons:

Property 1 (existence and uniqueness of the solution). The solutions of the SEIADR model exist and are uniquely defined for any given initial conditions and any given vaccination and antiviral controls and can be expressed with explicit formulas.

Property 2 (positivity of the solution). Assume that $V_0 \in [0, b_1]$ and ρ_D, $\rho_V : \boldsymbol{R}_{0+} \to [0,1]$. Then, the SEIADR model is "positive" in the sense that its trajectory solution is nonnegative for all time under non-negative initial conditions:

$$[min(S(0), E(0), I(0), A(0), R(0), D(0)) \geq 0] \Rightarrow [min(S(t), E(t), I(t), A(t), R(t), D(t)) \geq 0; \forall t \in \boldsymbol{R}_{0+}].$$

This property allows a potential validity of the model for its application to real epidemic disease spreads on populations in both presence and absence of eventually mixed vaccination-antiviral-corpses culling controls. The proof is organized by using contradiction arguments to some subpopulation value being the first one to reach the zero value at some nonzero time instant. It follows due to the chained coupling dynamics in-between sub-populations that this supposed zero value should have been reached at a former time instant.

Properties 3 (uniform boundedness of the solution):

(i) $\limsup_{t \to \infty} I(t) \leq b_1 / \alpha$ and $\sup_{t \in \boldsymbol{R}_{0+}} I(t) < +\infty$,

(ii) $N(t) < +\infty$; $\forall t \in \boldsymbol{R}_{0+}$,

(iii) $max\left(\sup_{t \in \boldsymbol{R}_{0+}} S(t), \sup_{t \in \boldsymbol{R}_{0+}} E(t) \sup_{t \in \boldsymbol{R}_{0+}} I(t), \sup_{t \in \boldsymbol{R}_{0+}} A(t), \sup_{t \in \boldsymbol{R}_{0+}} R(t), \sup_{t \in \boldsymbol{R}_{0+}} D(t) \right) < +\infty$.

where $N(t)$ is the total population obtained by summing up the values of all the subpopulations at each time instant. The proof is made in two parts: a) It is proved that the whole subpopulation is bounded from its differential time equation $\dot{N}(t) = -b_2 N(t) + b_1 - \alpha I(t)$; $\forall t \in \boldsymbol{R}_{0+}$, b) This above property together with the non-negativity of all the subpopulations for all time leads to the boundedness of all of those subpopulations for all time.

Properties 4 (existence and stability of the unique disease-free equilibrium periodic solution or equilibrium point): Assume that

1) $K_V^* < min(\mu, b_2 + min(\gamma, \tau_0, \eta))$,

2) the initial conditions of (1)-(6) to be non-negative, $V_0 \in [0, b_1]$, $0 < T_{min} \le T_i = t_{i+1} - t_i \le T_{max} < +\infty$; $\forall t_i \in ImpS \cup ImpI \cup Imp\,D$,

3) $\rho_D(t_i)(\in [0,1]) \to \rho_D^*$ as $t_i(\in ImpD) \to \infty$, $\rho_V(t_i)(\in [0,1]) \to \rho_V^*$ as $t_i(\in ImpS) \to \infty$, $\rho_\xi(t_i)(\in [0,1]) \to \rho_\xi^*$ as $(t_{i+1} - t_i) \to T_V^*$ $t_i(\in Imp\,I) \to \infty$ and $K_V(t) \to K_V^*$ as $t \to \infty$.

Then, the following properties hold:

(i) There exists a unique disease- free equilibrium periodic solution if $\rho_V^* \in [0,1)$ in the set *ImpS* of impulsive vaccination of the susceptible subpopulation, which is independent on the antiviral control, and which is defined by:

$$x_{df}^*(T_V^* + \sigma) := \left(S_{df}^*(T_V^* + \sigma), E_{df}^*, I_{df}^*, A_{df}^*, D_{df}^*, R_{df}^*(T_V^* + \sigma)\right)^T = \left(S_{df}^*(T_V^* + \sigma), ,0,0,0,0, R_{df}^*(T_V^* + \sigma),\right)^T$$

; $\forall \sigma \in [0, T_V^*]$, where

$$S(T_V^* + \sigma) = \lim_{t_i = nT_V^* (\in ImpS) \to \infty} S(t_i + \sigma) = \frac{b_2(b_1 - V_0) + \eta b_1}{b_2(b_2 + \eta + K_V^*)} + o\left(T_v^{*-1}\right) + o\left(\rho_V^*\right);\ \forall \sigma \in [0, T_V^*)$$

$$R(T_V^* + \sigma) = \lim_{t_i = nT_V^* (\in ImpS) \to \infty} R(t_i + \sigma) = \frac{b_2 V_0 + K_V^* b_1}{b_2(b_2 + \eta + K_V^*)} + o\left(T_v^{*-1}\right) + o\left(\rho_V^*\right);\ \forall \sigma \in [0, T_V^*)$$

$$S(T_V^*) = (1 - \rho_V^*) S(T_V^{*-}) \quad , \quad R(T_V^*) = (1 + \rho_V^*) R(T_V^{*-})$$

; $\forall t_i \in ImpS$ with an associated limit total population $N_{df}^* = S_{df}^*(\sigma) + R_{df}^*(\sigma) = \frac{b_1}{b_2} = \lim_{t \to \infty} N(t)$;

$\forall \sigma \in [0, T_V^*]$ and controls $\xi_{df}^* = \xi_0$, and

$$\lim_{n \to \infty} V(nT_V^* + \sigma) = V_{df}^*(T_V^* + \sigma) = V_0 + K_V^* S_{df}^*(T_V^* + \sigma) + \rho_V^* S_{df}^*(T_V^{*-}) \delta(\sigma - T_V^*)$$

; $\forall \sigma \in [0, T_V^*]$ where $\delta(.)$ is the Dirac distribution. If $\rho_V^* = 0$ or the impulsive vaccination ends in finite time then the periodic oscillation becomes a disease- free equilibrium point.

(ii) Assume that the extended disease transmission coefficient $\overline{\beta} = max(\beta, \beta_A, \beta_D)$ is small enough to satisfy $\overline{\beta} < \frac{1}{S_{df}^*} min\left(\mu, b_2 + min\left(K_V^*, \gamma, \tau_0, \eta\right)\right)$. Then, the linearized trajectory solution about the disease- free equilibrium point is locally asymptotically stable.

If $\overline{\beta} > \frac{1}{S_{df}^*} min\left(\mu, b_2 + min\left(K_V^*, \gamma, \tau_0, \eta\right)\right)$ then the linearized trajectory solution about the disease-free equilibrium point is locally unstable.

The main message of Properties 4 is the following: "If the extended disease transmission rate $\overline{\beta} = max(\beta, \beta_A, \beta_D)$ (typically $\overline{\beta} = \beta$ in practice) is small enough then the disease- free equilibrium point is globally asymptotically stable. As a result, the whole nonlinear model about such an equilibrium is also locally asymptotically stable". Note that under impulsive controls there is a jump from the left to the right in the values of the equilibrium periodic regime if the control impulses do not end after a finite time interval.

Property 5 (reproduction-like number): It is concluded from Property 4 (ii) that we can define $R_{df} = \dfrac{\overline{\beta} S_{df}^*}{min\left(\mu, b_2 + min\left(K_V^*, \gamma, \tau_0, \eta\right)\right)}$ as a disease- free reproduction-like number. If $R_{df} < 1$, or equivalently, if the infective disease transmission coefficient is small enough such that $\overline{\beta} < \dfrac{1}{S_{df}^{*-}} min\left(\mu, b_2 + min\left(K_V^*, \gamma, \tau_0, \eta\right)\right)$, then the disease does not spread for small deviations from the disease-free equilibrium. If $R_{df} > 1$, equivalently, if $\overline{\beta} > \dfrac{1}{S_{df}^*} min\left(\mu, b_2 + min\left(K_V^*, \gamma, \tau_0, \eta\right)\right)$then the equilibrium oscillation is locally asymptotically unstable.

Properties 6 (existence and uniqueness of the endemic equilibrium oscillation/point): (i) If the given assumptions for Properties 4 hold, then there is no endemic equilibrium point or limit periodic oscillation:

$$x_{end}^* := \left(S_{end}^*, E_{end}^*, I_{end}^*, A_{end}^*, D_{end}^*, R_{end}^*\right)^T$$

or equilibrium periodic solution , where $E_{end}^* \neq 0$, provided that $\underline{\beta} = min(\beta, \beta_A, \beta_D) < \beta_\delta$ for some existing some $\beta_\delta \in \boldsymbol{R}_+$. As a result, if $\overline{\beta} < min\left(\dfrac{1}{S_{df}^*} min\left(\mu, b_2 + min\left(K_V^*, \gamma, \tau_0, \eta\right)\right), \beta_m\right)$ for some $\beta_m (\leq \beta_\delta) \in \boldsymbol{R}_+$ then there only exists the disease-free equilibrium periodic solution or point in the particular of asymptotic removal of vaccination and antiviral impulsive controls, which is globally asymptotically stable.

(ii) Assume that $K_V(t) = K_\xi(t) = \rho_V(t) = \rho_\xi(t) = 0$; $\forall t \in \boldsymbol{R}_{0+}$. Then, the endemic equilibrium point, if it exists, is unique.

The endemic equilibrium periodic solution or endemic equilibrium point I in the case of asymptotic impulsive - free case) is characterized bi its exposed population to be nonzero, i.e. $E_{end}^* \neq 0$, what causes the asymptomatic and symptomatic infective endemic populations to be nonzero. Note that the endemic equilibrium periodic solutions or points make the disease to be permanent in the sense that the infective population cannot be asymptotically removed contrarily to the disease- free equilibrium points where the infection is asymptotically removed. This result establishes is that for small enough coefficient transmission rates only the disease- free equilibrium is relevant since the endemic one does not exist.

4. Example

It is now presented a set of numerical simulation work imnplemented in Matlab. The parameters of the

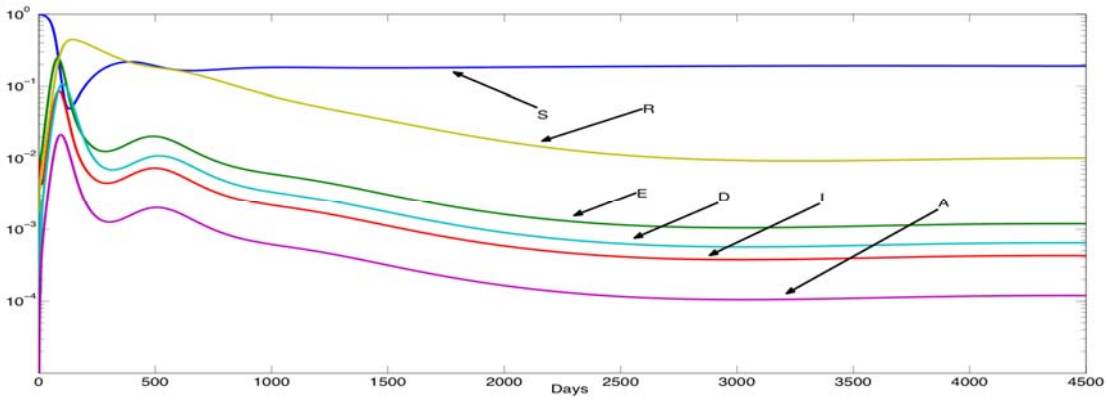


Figure 1. Endemic equilibrium reached for a dynamic without culling

model are obtained from real data from a study of Ebola disease [9]:
The recruitment rate and the natural average death rate are $b_1 = b_2$ =1/(70x365) days^{-1} so that the total population is normalized to unity while the disease transmission coefficients are β= 0.16, $\beta_A = 0.05, \beta_D = 0.5$ respectively. The average duration of the immunity period reflecting a transition from the recovered to the susceptible is determined by $1/\eta$ =1000 days, γ =1/15.8 days^{-1}, α =1/13.3 days^{-1}, τ_0 =1/12 days^{-1}, p =0.9, the average duration of infection $1/\mu$ =20 days and $V(t)$ and $\xi(t)$ are, respectively, constant values V=0.2b$_1$ and ξ =0.02.

First, a study is concerned with initial conditions $S(0) = S_{DFE}$, $R(0) = R_{DFE}$, $A(0) = E(0) = D(0) = 0$ and $I(0)$=0.01 without culling, or impulsive removal of the infectious diseases at regular times (fig.1). In Figure 1, it can be seen where the dynamic of the subpopulations is seen to evolve into a endemic equilibrium point, and the disease remains endemic. In Fig.2 the culling of a 95% of the infectious

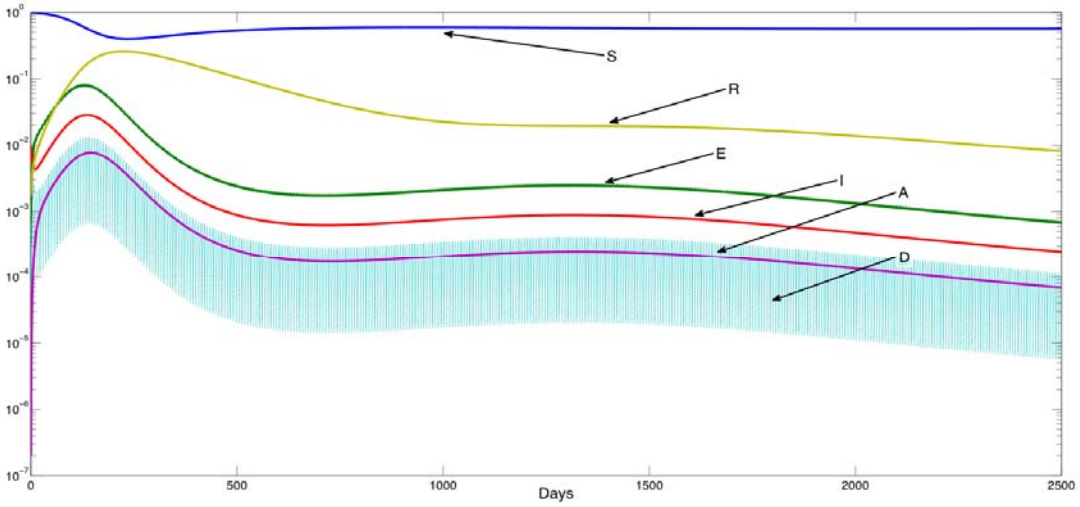


Figure 2. A dynamic with regular culling of 95% of D(t) subpopulation each 7 days

bodies performed regularly each week. In Figure 2 it can be seen how the values related to the sick subpopulations decrease exponentially, as the susceptible and the recovered subpopulation reach the disease-free equilibrium.

5. Concluding remarks

In this paper, the properties of a new proposed epidemic model which is referred to as an SEIADR epidemic model have been described. This model incorporates the asymptomatic infective and dead-infective populations and three class of optional controls (vaccination on the susceptible, antiviral treatment on the symptomatic infective- both of them can contain optional constant and feedback regular and impulsive actions- plus a culling action, which is impulsive by nature, on the lying effective corpses. The positivity and stability properties of the solution as well as the existence of the unique disease-free equilibrium point and the existence, non-existence and uniqueness (if it exists) of the endemic equilibrium point are investigated. The proposed model could be useful to deal with the propagation of the Ebola disease where lying un-recovered dead corpses are known to be also highly infective in urban areas with high- population density.

References

[1] Mollison D 1995 *Epidemic Models: Their Structure and Relation to Data, Publications of the Newton Institute, Cambridge University Press,* 1995, Denis Mollison Editor (transferred to digital printing 2003).
[2] Keeling MJ and P. Rohani P 2008 *Modeling Infectious Diseases in Humans and Animals*, Princeton University Press, Princeton and Oxford
[3] Bellan SE, Pulliam JRC, Dushoff J. and Meyers LA 2014, *The Lancet* **384** 9953 pp. 1499-1500
[4] Santermans E, Robesyn E, Ganiani T, Sudre B, Faes, C, Quinten, C, Van Bortel, W , Haber, T, Kovac F, Van Reeth F, Testa M, Hens N and Plachouras, D 2016 *Plos One* **11**(1), doi:101371/journal.pone.0147172
[5] Song XY, Jiang J and Wei HM 2009 *Applied Mathematics and Computation* **214**, pp. 381-390
[6] De la Sen M, Agarwal RP, Ibeas A and Alonso-Quesada S 2011 *Advances in Difference Equations*, **2011**, Article ID 748608, Vol. 2011, doi:10.1155/2011/748608
[7] De la Sen M, Agarwal RP, Ibeas A and Alonso-Quesada S 2010 *Advances in Difference Equations* **2010**, Article ID 281612, doi:10.1155/20101/281612
[8] De la Sen M and Alonso-Quesada S 2011 *Applied Mathematics and Computation* **218**, pp. 3888-3904
[9] Rivers CM, Lofgren ET, Marathe M, Eubank S, Lewis BL *PLOS Currents Outbreaks* **2014** Oct 16 . Edition 1. doi: 10.1371/currents.outbreaks.fd38dd85078565450b0be3fcd78f5ccf.