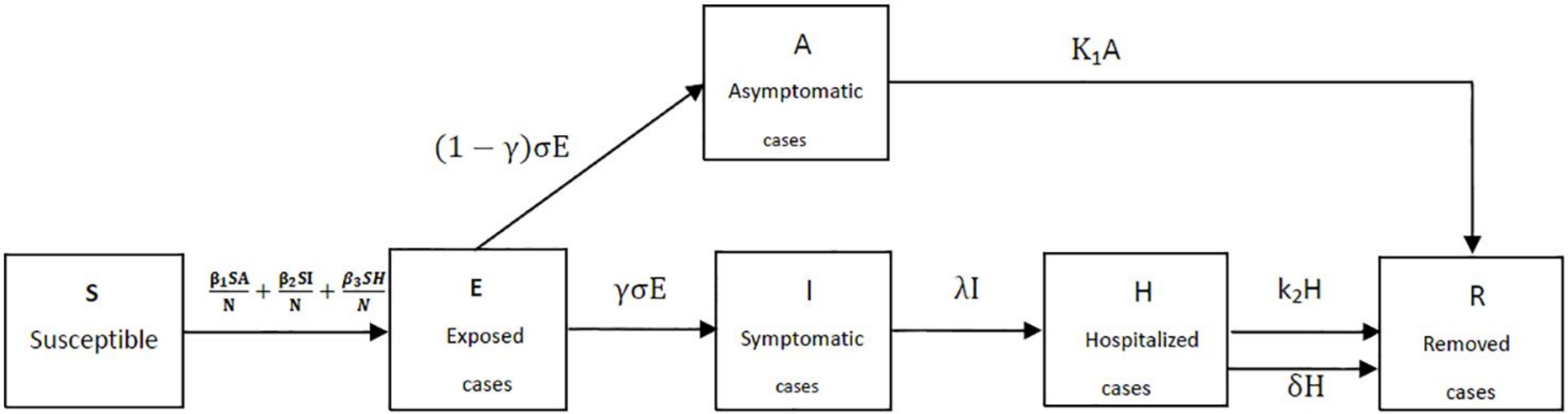
SEIAR Model with Vaccination on MERS 2015 Korea

By: Gia (Sahej) Ahuja, Rehan Chinoy, Christine Dai,
Tara Jaigopal, Hoony Kim, Sofia Tam

MERS-CoV

- a viral respiratory infection caused by Middle East respiratory syndrome–related coronavirus (MERS-CoV)
- first identified case in June 2012 in Jeddah, Saudi Arabia
- largest outbreak in Korea from May 20, 2015 to July 4, 2015, with a total of 186 cases and a death toll of 38.
- SEAIHR model by Zhi-Qiang Xia et al[1]

Flowchart of Xia et al.



Clinical Trial > Lancet Infect Dis. 2019 Sep;19(9):1013-1022. doi: 10.1016/S1473-3099(19)30266-X. Epub 2019 Jul 24.

Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial

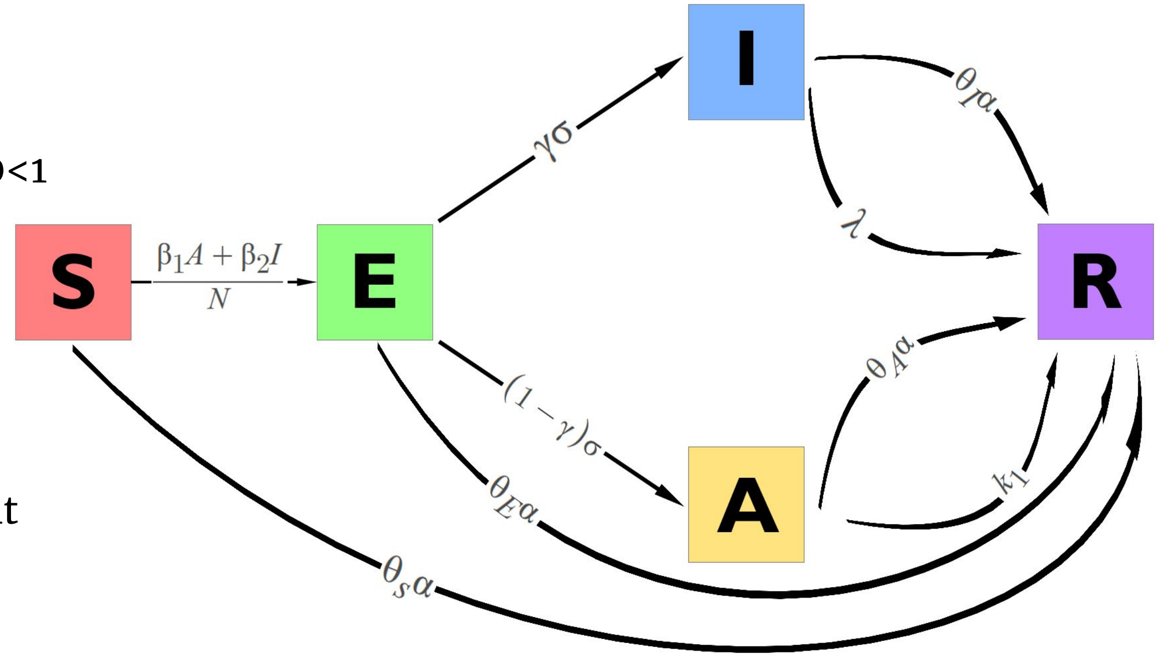
Kayvon Modjarrad, et al.

Interpretation: The GLS-5300 MERS coronavirus vaccine was well tolerated with no vaccine-associated serious adverse events. Immune responses were dose-independent, detected in more than 85% of participants after two vaccinations, and durable through 1 year of follow-up. The data support further development of the GLS-5300 vaccine, including additional studies to test the efficacy of GLS-5300 in a region endemic for MERS coronavirus.

Modified Flowchart

α: the daily vaccination rate
(variable!)

Goal: to find range of α so that R0<1



Assumptions:
1. Closed population
2. Daily vaccination rate constant
3. Vaccine works immediately

Modified Model

$$
\begin{cases}
\dfrac{dS}{dt} = -\dfrac{\beta_1 AS}{N} - \dfrac{\beta_2 IS}{N} - \theta_S \alpha S \\
\dfrac{dE}{dt} = \dfrac{\beta_1 AS}{N} + \dfrac{\beta_2 IS}{N} - \sigma E - \theta_E \alpha E \\
\dfrac{dI}{dt} = \gamma \sigma E - \lambda I - \theta_I \alpha I \\
\dfrac{dA}{dt} = (1-\gamma)\sigma E - k_1 A - \theta_A \alpha A \\
\dfrac{dR}{dt} = \theta_S \alpha S + \theta_E \alpha E + k_1 A + \theta_A \alpha A + \lambda I + \theta_I \alpha I
\end{cases}
$$

Analyzing Stability

Theorem 1 *An equilibrium point* $\mathbf{x}^*$ *of the differential equation 1 is stable if all the eigenvalues of* $\mathbf{J}^*$*, the Jacobian evaluated at* $\mathbf{x}^*$*, have negative real parts.* [7]

$$\begin{cases} -\frac{\beta_1 AS}{N} - \frac{\beta_2 IS}{N} - \theta_S \alpha S = 0 \\ \frac{\beta_1 AS}{N} + \frac{\beta_2 IS}{N} - \sigma E - \theta_E \alpha E = 0 \\ \gamma \sigma E - \lambda I - \theta_I \alpha I = 0 \\ (1-\gamma)\sigma E - k_1 A - \theta_A \alpha A = 0 \\ \theta_S \alpha S + \theta_E \alpha E + \theta_I \alpha I + \theta_A \alpha A + k_1 A + \lambda I = 0 \end{cases} \longrightarrow$$

Constraints:

$$\begin{cases} S + E + I + A + R = N \\ S,\ E,\ I,\ A,\ R \geq 0 \end{cases}$$

$$\downarrow$$

Equilibrium Point:

$$\mathrm{X} = (0,\ 0,\ 0,\ 0,\ \mathrm{N})$$

$$X' = (0, 0, 0, 0)$$

Analyzing Stability

Theorem 1 *An equilibrium point* $\mathbf{x}^*$ *of the differential equation 1 is stable if all the eigenvalues of* $\mathbf{J}^*$*, the Jacobian evaluated at* $\mathbf{x}^*$*, have negative real parts.* [7]

$$J = \begin{pmatrix} -\frac{\beta_1 A}{N} - \frac{\beta_2 I}{N} - \theta_S \alpha & 0 & -\frac{\beta_2 S}{N} & -\frac{\beta_1 S}{N} \\ \frac{\beta_1 A}{N} + \frac{\beta_2 I}{N} & -\sigma - \theta_E \alpha & \frac{\beta_2 S}{N} & \frac{\beta_1 S}{N} \\ 0 & \gamma\sigma & -\lambda - \theta_I \alpha & 0 \\ 0 & (1-\gamma)\sigma & 0 & -k_1 - \theta_A \alpha \end{pmatrix}$$

$$X' = (0,0,0,0) \quad \longrightarrow \quad J_X = \begin{pmatrix} -\theta_S \alpha & 0 & 0 & 0 \\ 0 & -\sigma - \theta_E \alpha & 0 & 0 \\ 0 & \gamma\sigma & -\lambda - \theta_I \alpha & 0 \\ 0 & (1-\gamma)\sigma & 0 & -k_1 - \theta_A \alpha \end{pmatrix}$$

Analyzing Stability

Theorem 1 *An equilibrium point* $\mathbf{x}^*$ *of the differential equation 1 is stable if all the eigenvalues of* $\mathbf{J}^*$*, the Jacobian evaluated at* $\mathbf{x}^*$*, have negative real parts.* [7]

$$J_X = \begin{pmatrix} -\theta_S\alpha & 0 & 0 & 0 \\ 0 & -\sigma-\theta_E\alpha & 0 & 0 \\ 0 & \gamma\sigma & -\lambda-\theta_I\alpha & 0 \\ 0 & (1-\gamma)\sigma & 0 & -k_1-\theta_A\alpha \end{pmatrix}$$

$$\lambda_1 = -\theta_S\alpha$$
$$\lambda_2 = -\sigma - \theta_E\alpha$$
$$\lambda_3 = -\lambda - \theta_I\alpha$$
$$\lambda_4 = -k_1 - \theta_A\alpha$$

$\longrightarrow$ **Stable**

R_0 : The Basic Reproduction Number

R0 is defined as the expected number of cases directly generated by one case in a population.

- $R_0 < 1$: the disease will eventually die out.
- $R_0 = 1$: the disease is stable.
- $R_0 > 1$: the disease will spread. [5]

How to find R_0: Next Generation Matrix

The next generation matrix: $\mathbf{FV^{-1}}$ $\Rightarrow$ Find spectral radius (the largest eigenvalue)

$\mathcal{F}$: the rate at which new infections appear
$\mathcal{V}$: the rate of transfer of individuals.

$$\mathcal{F} = \begin{pmatrix} \frac{\beta_1 AS}{N} + \frac{\beta_2 IS}{N} \\ 0 \\ 0 \end{pmatrix} \text{ and } \mathcal{V} = \begin{pmatrix} \sigma E + \theta_E \alpha E \\ -(1-\gamma)\sigma E + k_1 A + \theta_A \alpha A \\ -\gamma\sigma E + k_2 I + \theta_I \alpha I \end{pmatrix}$$

Calculating R0:

We let our new $\mathcal{F}$ and $\mathcal{V}$ denote the Jacobian matrices of $\boldsymbol{F}$ and $\boldsymbol{V}$ about (E, A, I).

$$F = \begin{pmatrix} 0 & \frac{\beta_1 S}{N} & \frac{\beta_2 S}{N} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \text{ and } V = \begin{pmatrix} \sigma + \theta_E \alpha & 0 & 0 \\ -(1-\gamma)\sigma & k_1 + \theta_A \alpha & 0 \\ -\gamma\sigma & 0 & \lambda + \theta_I \alpha \end{pmatrix}$$

However, for our starting point, we assume that the number of susceptible people is equal to **N** the total population.

Initial point: **(S,E,A,I,R) = (N,0,0,0,0).**

$$F = \begin{pmatrix} 0 & \beta_1 & \beta_2 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \qquad V = \begin{pmatrix} \sigma + \theta_E \alpha & 0 & 0 \\ -(1-\gamma)\sigma & k_1 + \theta_A \alpha & 0 \\ -\gamma\sigma & 0 & \lambda + \theta_I \alpha \end{pmatrix}$$

Calculating R0:

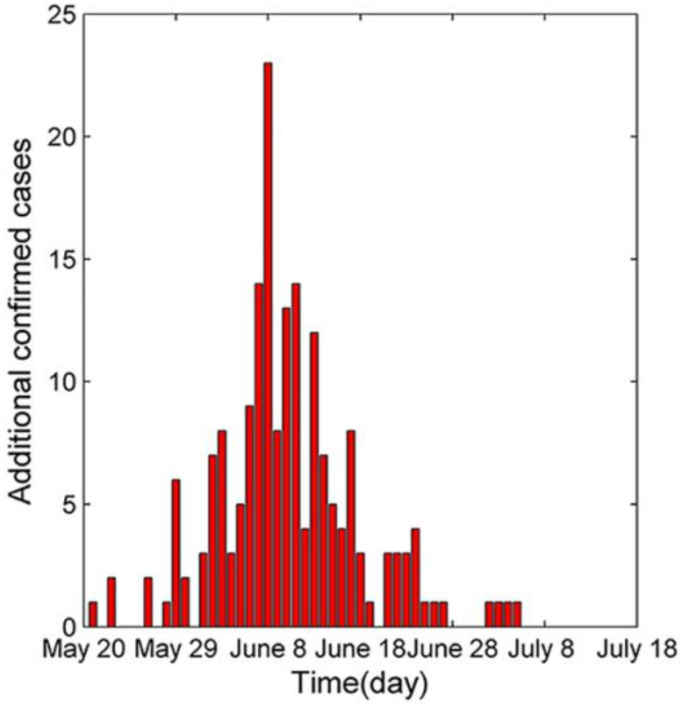
$$FV^{-1} = \begin{pmatrix} \frac{-\beta_1\sigma(\gamma\lambda - \lambda + \theta_I(\alpha\gamma - \alpha)) + \beta_2\sigma\gamma(\theta_A\alpha + k_1)}{(\theta_A + k_1)(\sigma\lambda + \theta_E\alpha\lambda + \theta_I(\theta_E\alpha^2 + \sigma\alpha))} & \frac{\beta_1}{\theta_A\alpha + k_1} & \frac{\beta_2(\sigma + \alpha\theta_E)}{\sigma\lambda + \theta_E\lambda + \theta_I(\theta_E^2 + \sigma\alpha)} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

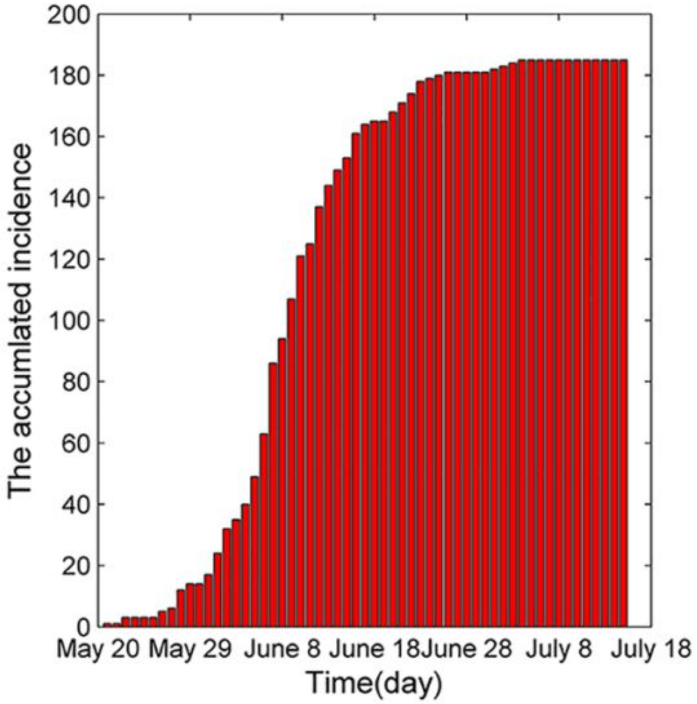
$$R_0 = \frac{-\beta_1\sigma\gamma\lambda - \beta_1\sigma\gamma\alpha\theta_I + \beta_1\sigma\lambda + \beta_1\sigma\alpha\theta_I + \beta_2\sigma\gamma\theta_A\alpha + \beta_2\sigma\gamma\lambda}{(\theta_E\alpha + \sigma)(\lambda + \alpha\theta_I)(\theta_A\alpha + \lambda)}$$

Assume that $\theta_S = \theta_E = \theta_I = \theta_A = \theta$

$$R_0 = \frac{-\beta_1\sigma\gamma\lambda - \beta_1\sigma\gamma\alpha\theta + \beta_1\sigma\lambda + \beta_1\sigma\alpha\theta + \beta_2\sigma\gamma\theta\alpha + \beta_2\sigma\gamma\lambda}{(\theta\alpha + \sigma)(\lambda + \alpha\theta)(\theta\alpha + \lambda)}$$

Two Stages: Before and After Control Measures





Stage I: May 20, 2015 – June 8, 2015

symbol	value
β_1	$.8756$
β_2	$.7833$
γ	$.0348$
θ	$.85$
σ	$\approx .1923$
k_1	$.2$
λ	$\approx .2$

In solving for $\boldsymbol{\alpha_1}$ when R0 < 1 we get:

$$1 > \frac{.14260...(\alpha_1) + .03423...}{.614125...(\alpha_1^3) + .43097...(\alpha_1^2) + .10078...(\alpha_1) + .00785}$$

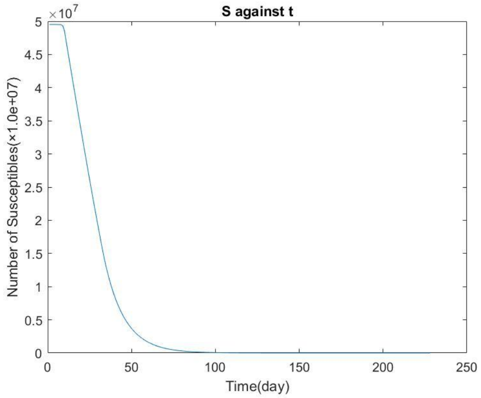
$$614125...(\alpha_1^3) + .43097...(\alpha_1^2) + .10078...(\alpha_1) + .00785 > .14260...(\alpha_1) + .03423...$$

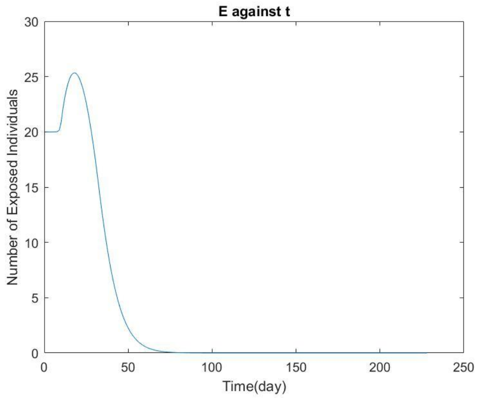
$$\approx$$

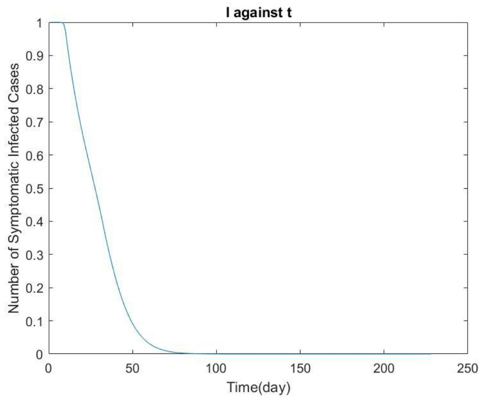
$$.614125\alpha_1^3 + .43097\alpha_1^2 - .04182\alpha_1 - .02638 > 0$$

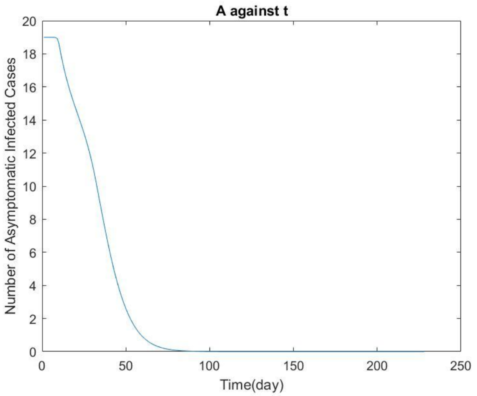
$$\alpha_1 > 0.25105$$

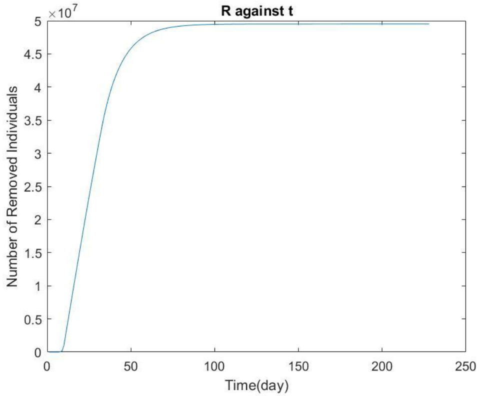
Stage I: May 20, 2015 – June 8, 2015











Stage II: June 9, 2015 - July 5, 2015

symbol	value
β_1	.83424
β_2	.0510
γ	.5377
θ	.85
σ	$\approx .1923$
k_1	.2
λ	$\approx .2$

In solving for $\boldsymbol{\alpha_2}$ when $R_0 < 1$ we get:

$$1 > \frac{.06752...(\alpha_2) + .01619...}{.614125...(\alpha_2^3) + .43097...(\alpha_2^2) + .10078...(\alpha_2) + .00785}$$

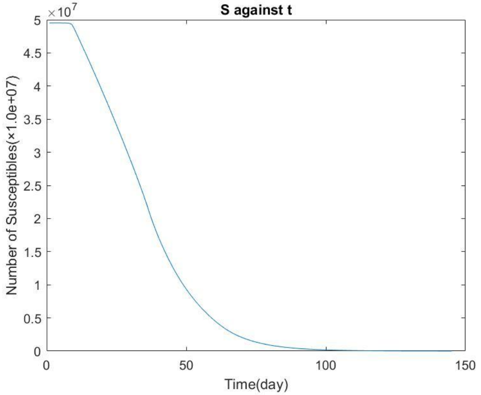
$$614125...(\alpha_2^3) + .43097...(\alpha_2^2) + .10078...(\alpha_2) + .00785 > .06752...(\alpha_2) + .01619...$$

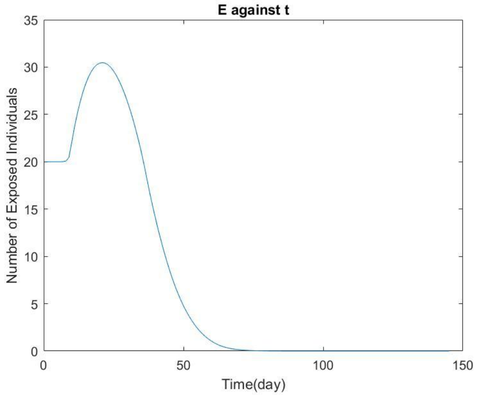
$$\approx$$

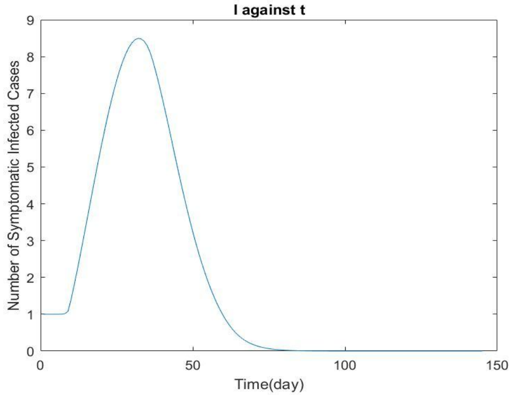
$$.614125\alpha_2^3 + .43097\alpha_2^2 - .03326\alpha_2 - .00905 > 0$$

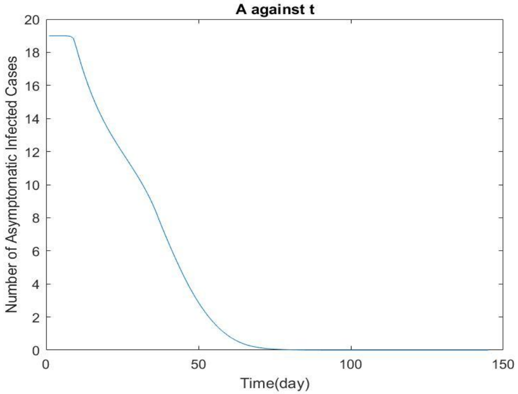
$$\alpha_2 > .10566$$

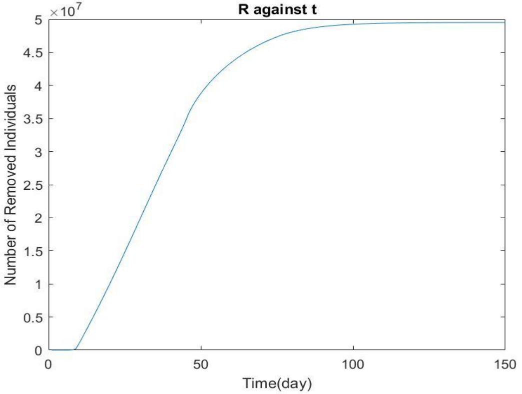
Stage II: June 9, 2015 - July 5, 2015











Conclusion

- **Summary:** The minimum vaccination rate is higher ($\alpha_1 > \alpha_2$) in the early stages of the epidemic (when control measures haven't yet been set in place) in order for the disease to die out.

Conclusion

- **Possibility for Further Investigation:**

  -using R instead of R_0

  -vaccination rate varies every day

References

1. Xia, Zhi-Qiang, et al. “Modeling the Transmission of Middle East Respirator Syndrome Corona Virus in the Republic of Korea.” PLOS ONE, vol. 10, no. 12, 2015, https://doi.org/10.1371/journal.pone.0144778.

2. Ghostine, Rabih, et al. “An Extended SEIR Model with Vaccination for Forecasting the COVID-19 Pandemic in Saudi Arabia Using an Ensemble Kalman Filter.” Mathematics, vol. 9, no. 6, 2021, p. 636., https://doi.org/10.3390/math9060636.

3. Phitchayapak Wintachai, Kiattisak Prathom. ”Stability analysis of SEIR model related to efficiency of vaccines for COVID-19 situation”, Heliyon, Volume 7, Issue 4, 2021, e06812, ISSN 2405-8440, https://doi.org/10.1016/j.heliyon.2021.e06812.

4. Modjarrad K, et al. ”Safety and immunogenicity of an anti-Middle East respiratory syndrome coronavirus DNA vaccine: a phase 1, open-label, single-arm, dose-escalation trial”. Lancet Infect Dis. 2019 Sep;19(9):1013-1022. doi: 10.1016/S1473-3099(19)30266-X. Epub 2019 Jul 24. PMID: 31351922; PMCID: PMC7185789.

5. Ramirez, Vanessa Bates. “What Is R0? Gauging Contagious Infections.” Healthline, Healthline Media, 20 Apr. 2020, https://www.healthline.com/health/r-naught-reproduction-number.

6. Adam, David. “A Guide to R - the Pandemic’s Misunderstood Metric.” Nature News, Nature Publishing Group, 3 July 2020, https://www.nature.com/articles/d41586-020-02009-w.

7. Roussel, Marc R. 2005, Stability Analysis for ODEs.

8. Diekmann, O et al. “The construction of next-generation matrices for compartmental epidemic models.” Journal of the Royal Society, Interface vol. 7,47 (2010): 873-85. doi:10.1098/rsif.2009.0386