University of Cape Town

STA5003W

Mathematical Modelling of Infectious Diseases

A Mobility Model for Measles Transmission in the DRC
Kinshasa Province Case Study

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Contents

1 Policy Brief

Measles transmission in Kinshasa province over 2 years was simulated as a case study to inform MCV1 distribution policy in the DRC. A compartmental mobility model was implemented with simulated values used to represent parameters which were unknown. The overarching goal of the study was to develop a model framework which could be extended to other provinces in the DRC with the adjustment of mobility matrix parameters and population estimates. In addition, the study aimed to gain some insight into the role of mobility networks and population structures in the transmission of measles in the province. In particular, the study aimed to gain insight in the role of vaccine administration intervention within this framework.

The model revealed an intuitive truth. Larger cities which are typically directly connected to smaller remote localities (via transport network) require higher vaccination coverage to newborns to mitigate against extreme vaccination incidence. Among lower populated localities, the vaccination coverage required appears to be linked to the number of other localities in direct connection with the locality in question. This is a rule of thumb which can be used to inform MVC1 distribution in the short-term.

The ability to determine actual vaccination coverage (and resulting MCV1 distribution) is underpinned by the presence of real data and parameters which have been rigorously estimated (using distributions etc.). Neither were available for the Kinshasa province. However, the model structure could be used to estimate parameters if population and incidence data pertaining to the province is supplemented.

2 Introduction

The following report studies the measles endemic in the Democratic Republic of Congo (DRC). Particular attention will be drawn to the Kinshasa Province, which contains the capital city, Kinshasa. The report will simulate measles transmission in the province using a metapopulation S(V)EIR model in an attempt to capture the affect of the interplay between small villages and large cities in the spread of measles. Further, we have accounted for social interactions between two age groups within the population, namely children (aged 0-15) and adults (aged 16+). This complexity is added to incorporate the effect of children, who are the primary vectors in measles transmission. This model will then be used to inform a resource allocation study on the distribution of MCV1 vaccines in the province over the 2 yeara period.

3 Literature Review

In 2010 the World Health Assembly (WHA) set out three milestones for control of the disease to be met by 2015 [3].

1. Increase regional MCV1 coverage to at least 90%, and to at least 80% by district.
2. Reduce yearly global measles incidence to less than 5 cases per million.
3. Reduce global measles fatality by at least 95% against the 2000 estimate.

The World Health Organisation (WHO) set out an objective to eliminate measles in four of its regions by 2015, and in all six of its regions by or before 2020. Measles elimination is defined as the absence of endemic measles virus transmission for a period greater than 12 months, as well as meeting surveillance criterion and key performance indicators. The strategy towards this objective was developed by the Measles and Rubella Initiative, who published *Global Measles and Rubella Strategic Plan, 2012–2020*, referred to as *The Plan* [21]. The publication laid out five core strategies.

1. Achieve and maintain high levels of population immunity by providing high vaccination coverage with two doses of measles- and rubella-containing vaccines.
2. Monitor disease using effective surveillance, and evaluate programmatic efforts to ensure progress.
3. Develop and maintain outbreak preparedness, respond rapidly to outbreaks and manage cases.
4. Communicate and engage to build public confidence and demand for immunization.
5. Perform the research and development needed to support cost-effective operations and improve vaccination and diagnostic tools.

The progress of *The Plan* was measured against the three milestones above, none of which were met by 2015 [14]. Furthermore, a 2017 report revealed that by 2015 these goals had not been met, and that measles had been eliminated in only one WHO region [3].

This study aims to address the 5th core strategy in *The Plan* through modelling. SEIR-type models are routinely used in the modelling of measles, for example by Peter (2018) [15] who sought to determine the disease-free equilibrium (DFE) and the endemic equilibrium (EE). This followed Bolarian's (2014) [10] proposition the use of a stochastic S(V)EIR model with an added vaccination component. This model determined the vaccination coverage required to eradicate measles.

A number of models have been built to simulate measles transmission in African countries. For example, Fred et al. (2014) [13] modelled the control of measles by vaccination in Kenya. Anes (2012) [6] modelled measles transmission in Ghana.

4 Problem Statement and Research Question

A global measles outbreak occurred in 2018, with the five countries with highest incidence (Democratic Republic of the Congo (DRC), Liberia, Madagascar, Somalia and Ukraine) accounting for nearly half the cases worldwide [22]. Poverty is cited as one of the main contributors to these outbreaks around the world, which lead to deaths which are entirely preventable through vaccination [21]. This is certainly relevant to the DRC. In addition, the country faces the challenge of damaged health systems as a result of years of conflict [12]. Resources are limited, which heightens the importance of investigating how these could be best distributed in areas in this country. Of particular interest in this study is the role of movement between larger cities with smaller, remote villages in its surrounds in the spread of the disease.

For this study we will focus on the Kinshasa province, since it contains the densely populated capital city surrounded by clusters of remote villages. The control method under investigation is the admin-

istration of MCV1 vaccination to newborns. The transmission of measles within this province will be simulated, and used to inform vaccination allocation strategy over the next two years.

The study is exploratory in nature, and aims to gain an understanding on the contributing factors in the transmission of measles in the mobility structure of Kinshasa to inform decision making within the province. It is intended that the model built is flexible enough to be adjusteed to other provinces in the DRC, but specific enough to capture the characteristics that are central to transmission in the country.

5 Kinshasa Province

The Kinshasa province is populated by approximately 14.3 million [2] inhabitants 11 million [1] of which reside in the capital city and surrounds according to the latest available data. The remaining occupants are distributed among the many remote villages in the province [11] (see Figure 2, Appendix). Inter-village travel between nearby villages occurs frequently on a daily basis [11]. It was hence decided to divide these villages into four clusters (or patches) which are ilustrated in Figure 2 (Appendix).

6 Model Building

6.1 S(V)EIR Model

The model used combines a metapopulation model approach [7] with an S(V)EIR model [10]. The metapopulation aspect will capture the inter-patch movements of individuals. The heterogeneity of transmission behaviour of children vs. adults will be captured using a mobility model based on previous work done by Appolloni (2014) [7], who proposed the model for distinguishing age groups in modeling the spread of the H1N1 pandemic in 2009. This is illustrated in Figure 4.

Suppose the Kinshasa province population is subdivided into patches as depicted in Figure 2 (see Appendix). Further, within each patch, we assume the population is subdivided into five compartments: Susceptible (S), Vaccinated (V) , Exposed (E), Infected (I), and Recovered (R).

We assume each patch is homogeneous in terms of parameters and age distribution. The population of each patch will be subdivided into adults and children within the five components. A transmission matrix approach will be used to account for movement between localities, as well as transmission between the two age groups [7].

The following differential equations define the S(V)EIR model for each patch $i \in I = \{1, 2, 3, 4\}$, and each age group $j \in J = \{1, 2\}$. Note that birth rates only apply for the 0-15 age band, that is, for $j = 1$. Further, given that we assume the vaccine is administered at birth (or shortly thereafter), inflow of newborns occurs at the vaccination component, V. This outlook is adopted from Bolarian [10]. The structure of the model is illustrated in Figure 1. The relevant parameters are described in Table 1.

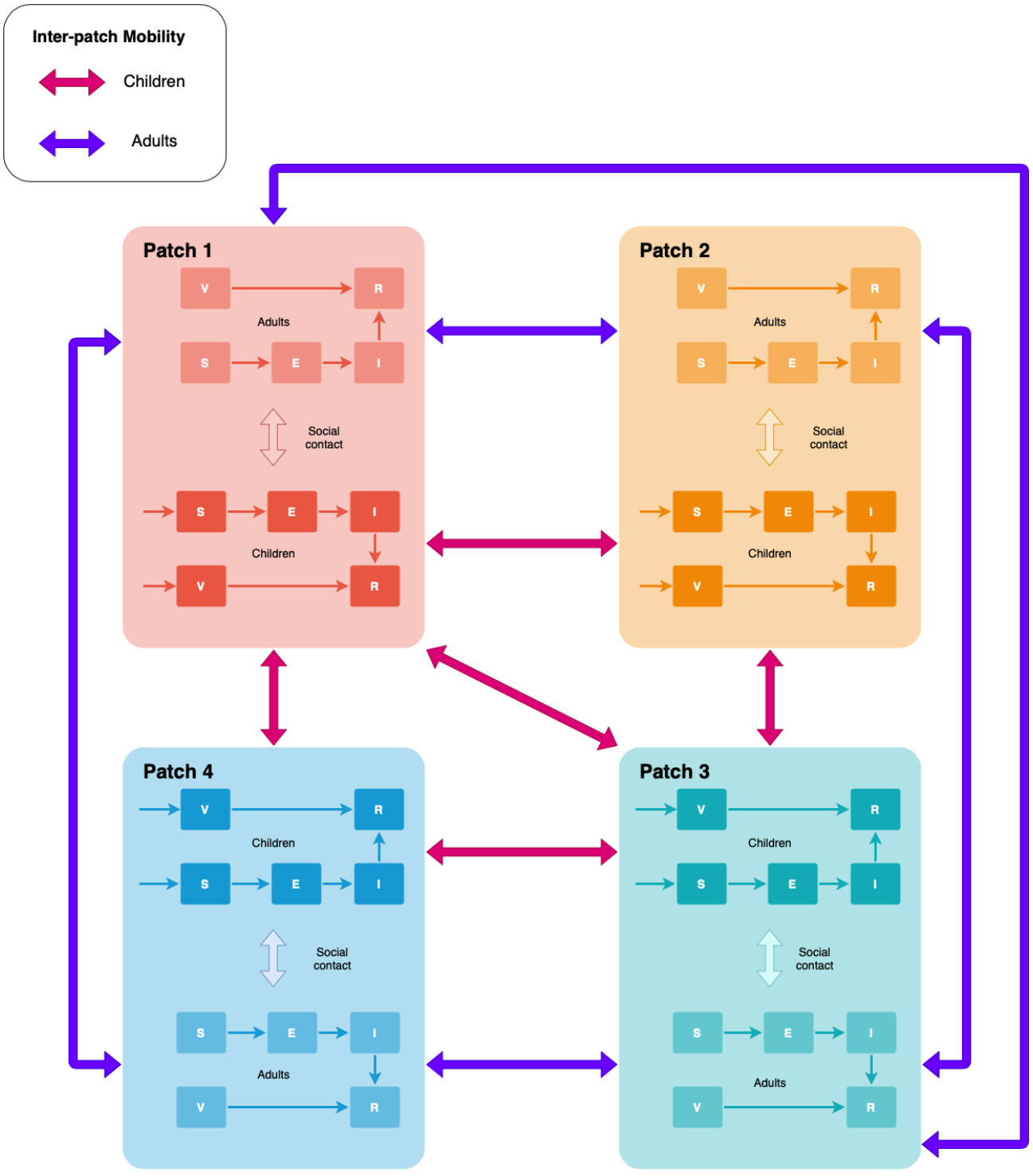

Figure 1: Model scheme

$$\frac{dS_{ij}}{dt} = \mu(1-\eta_i)N_{ij}\mathbb{1}_{\{j=1\}} - \frac{\beta I_{ij}S_{ij}}{N_{ij}}\sum_{l\in I}\delta_{lj} - \alpha S_{ij} + \sum_{k\in I}S_{kj}\theta_{kj} - S_{ij}\sum_{l\in I}\theta_{il}$$

$$\frac{dV_{ij}}{dt} = \mu\eta_i N_{ij}\mathbb{1}_{\{j=1\}} - (\alpha+\kappa)\,V_{ij} + \sum_{k\in I}V_{kj}\theta_{ki} - V_{ij}\sum_{l\in I}\theta_{il}$$

$$\frac{dE_{ij}}{dt} = \frac{\beta I_{ij}S_{ij}}{N_{ij}}\sum_{l\in I}\delta_{lj} - (\varepsilon+\alpha)E_{ij} + \sum_{k\in I}E_{kj}\theta_{ki} - E_{ij}\sum_{l\in I}\theta_{il}$$

$$\frac{dI_{ij}}{dt} = \varepsilon E_{ij} - (\gamma+\alpha+\varphi)I_{ij} + \sum_{k\in I}I_{kj}\theta_{ki} - I_{ij}\sum_{l\in I}\theta_{il}$$

$$\frac{dR_{ij}}{dt} = \gamma I_{ij} - \alpha R_{ij} + \kappa V_{ij} + \sum_{k\in I}R_{kj}\theta_{ki} - R_{ij}\sum_{l\in I}\theta_{il}$$

The model was executed using time-steps of one month for 24 months. The choice of time-steps is motivated by the reality that it is unlikely that distribution can be planned on the weekly/daily basis. The ODE's were evaluated at each time-step using the `deSolve` package in `R` [17]. It is assumed that there is no movement between the two age groups during this time, since this would likely be insignificant.

6.1.1 Starting Values

The starting values of the ODE's were estimated using measles surveillance data from WHO [19] [20]. The starting value for R was approximated using the most recent vaccination coverage value [19]. The starting value for I was approximated using the most recent available reported case value for the DRC [20] by adjusting for the population of the province as a ratio of the total country population. This adjusted cases value was distributed among the patches under a few assumptions. It is assumed that in general the children group have twice the number of cases than the adult groups per capita per patch, and that the group of children who reside in the capital city have twice the number of cases as other children. Hence, patches 2-4 have the same number of cases among children per capita, and patch 1 has double that proportion of cases in children per capita. Each patch has the same number of cases among adults per capita. It is assumed that the starting values for E and V components are each 0, since the time spent in these components in relatively small.

Table 1: Description of Model Parameters

	Description	Unadjusted value (from source)	Adjusted value (monthly per capita)	Source
μ	Birth rate	40.6 per 1000 per year	0.003383333	[8]
α	Natural death rate	9.3 per 1000 per year	0.000775	[9]
ϕ	Death rate due to infection	0.125 per year	0.01041667	[13]
κ	Rate of immunity after vaccination	0.14286 per year	0.01041667	[18]
β	Transmission probability	0.09091	0.09091	[6]
γ	Recovery rate from I	21 days after initial infection	3.33333 (using 21 days)	[15] [5]
ϵ	Rate of infectiousness after E	10-12 days after initial infection	2.5 (using 12 days)	[5]
η_i	Vaccination coverage in patch i (newborns)	currently 0.92 (to be adjusted in resource allocation)	decision variable	[19]
δ_{kl}	Number of contacts between members of group k and l	variable across k, l	variable across k, l	social contact matrix (simulated)
θ_{kl}	Monthly travel rate from patch k to l	variable across k, l	variable across k, l	mobility matrix approximated using [16]

6.1.2 Mobility and Contact Matrices

The matrix was simulated by drawing a random uniform number to approximate the average rate of input and output per patch per day, and then converting to a monthly estimate, e. The matrix is then derived from the proximity shown in the map in Figure 2 (Appendix). All patches are accessible from one another except the pair 2 and 4.

$$\Delta = \begin{pmatrix} 1 & e & e & e \\ e & 1 & e & 0 \\ e & e & 1 & e \\ e & 0 & e & 1 \end{pmatrix} \tag{1}$$

The parameters used for the social layer of the model (in the social contact matrix) were sourced from Prem (2017) [16] using the estimates for Congo as approximations, since DRC estimates were unavailable. The "all locations matrix" was used. The contact matrix gives us daily contacts per individual in 5 year age bands, which were grouped into the two age bands of interest (0-15, 16+ years) by taking sums. Thereafter, this had to be converted to a monthly estimate before use in the model.

6.2 Non-Linear Program (NLP) for Allocation of Vaccine Resources

To gain insight into the optimal allocation of vaccines across the four patches, a NLP was used. Suppose we have a finite number of vaccinations available for the 2 year period, v_{max}. Suppose further, we assume the public health decision-makers adopt a risk-averse approach in which they aim to minimise the maximum number of infectious individuals at any given time point over the two year period. This outlook is taken to avoid exhuaasting treatment resources. Recall that η_i is the vaccination rate for patch i. Define P_i as the population of patch i. We approximate the number of births over the 2 year period as $24\mu \sum_{i \in I} P_i$. Hence, the number of vaccinations to be administered over the two year period can be approximated as $24\mu \sum_{i \in I} P_i \eta_i$. Hence, the following NLP was constructed.

$$\begin{aligned} \text{d.v} \quad & \eta_i \\ \min. \quad & \max_{t \in T} \left\{ \sum_{j \in J} I_{ij}(t) \right\} \\ \text{s.t} \quad & 24\mu \sum_{i \in I} P_i \eta_i \leq v_{max} \\ \text{where} \quad & \eta_i \in [0, 1] \\ & i \in \{1, 2, 3, 4\} \\ & J = 1, 2 \\ & T = \{1, 2, ..., 24\} \end{aligned}$$

Where $I_{ij}(t)$ arises from the simulation. We assume consistent population in each of the patches over the two year period and hence consistent birthrate. This was done for purposes of simplicity of the

optimisation, which is time consuming to solve even in this simplified form. The optimisation problem was solved in `R` using the `nloptr` package [23], which is a package designed for solving NLP's using various algorithms.

7 Results

The results in Table 2 arose from the NLP solution using $v_{max} = 80\ 000$. Intuitively, the results make sense. Given that Patch 1 is linked in the mobility matrix to all other patches, it seems fitting that the highest vaccination coverage is required, since larger numbers of individuals enter and exit the city to other patches than any other patch.

Table 2: NLP Solutions

	Patch 1 (capital)	Patch 2	Patch 3	Patch 4
η_i	0.90	0.39	0.62	0.48

The resulting S(V)EIR components are depicted in Figures 5 to 8 (Appendix).

8 Sensitivity Analysis

Given that the parameters used to obtain the solutions are imperfect point estimates, it needs to be assessed how the solutions may vary using a range of parameters. There is some uncertainty associated with the model results which need to be accounted for.

The value used for transmission probability, β is taken from a similar study done in Ghana [6], and may well be inaccurate. This parameter is somewhat dependent on human behaviour, which means variability could be high from country to country and even day-to-day. Ten different values were tested in the optimal model. Two extremes are depicted in Figures 9 and 10 (see Appendix). As β increases, there is a increase in rate of initial infectious population, however there is very little change in the model output at steady state.

Perhaps the most contentious the parameters used in the model are the rate of recovery, γ, and rate of infectiousness, ϵ given that ϵ is provided as a range in the literature [5], and γ is dependent on ϵ. The range of number of days spent in incubation was explored, with each corresponding γ. The results are depicted in Figures 11 and 12 (Appendix). The plots show similar transmission patterns across both variants, and similar results at steady state. Hence, the sensitivity of the model to both sets of parameters is low.

9 Weaknesses

Some of the weaknesses in the model have been addressed, however there are many more which should be mentioned. For example, the model does not capture inter-provincial travel in the DRC, which

largely occurs along the Congo River for trade purposes [11]. However, this additional complexity is assumed to be unimportant, since children are the primary vectors for measles transmission. Furthermore, inter-village (intra-patch) mobility is not accounted for.

A major weakness of the model is the absence of the MCV2 vaccination component. The model built by Bolarian [10] for the spread of measles in Nigeria, MCV2 was omitted since the country's policy is to provide a single dose vaccination through public health systems. There is little information publicly available on vaccination policy in the DRC. Hence, it was assumed that a single MCV1 dose was also relevant in this context, although this might not be the case.

It should also be noted that the seasonal effect of school terms was not captured in the model. However, this effect may be of little significance int his context, given that approximately 40% of school-aged children in the DRC are not enrolled in school [11].

Additionally, it should be noted that the model we have built arises from imperfect data. Census data on the villages in Kinshasa province were not found, and their populations were simulated for the purpose of the case study. Furthermore, there is little information publicly available regarding the rate at which travelling occurs in the mobility network. This was also simulated.

Another weakness in the model is the absence of stochasticity in the NLP optimisation. This would require more sophisticated optimisation techniques which would be able to handle a more complex problem. Further, we have not tested that the solution obtained in the NLP is in fact a global minima.

10 Conclusion

The simulation of measles transmission using a layered metapopulation S(V)EIR model has determine that the vaccination coverage in clusters of large cities surrounded by remote villages should be informed by the mobility structure and populations of these patches. Highly populated patches require higher vaccination coverage on newborn children than less populated patches. Furthermore, the number of patches having direct mobility connection to a certain patch will effect the vaccination coverage required. Although the model built is imperfect, it appears to capture the features of interest to the research question. A similar model could be implemented using mobility structures in other provinces in DRC to inform vaccination coverage policy. Despite being a deterministic model, the results of the simulation do not reflect accurate policy guidelines, since important inputs such as patch populations were simulated.

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11 Appendix

11.1 DRC Background

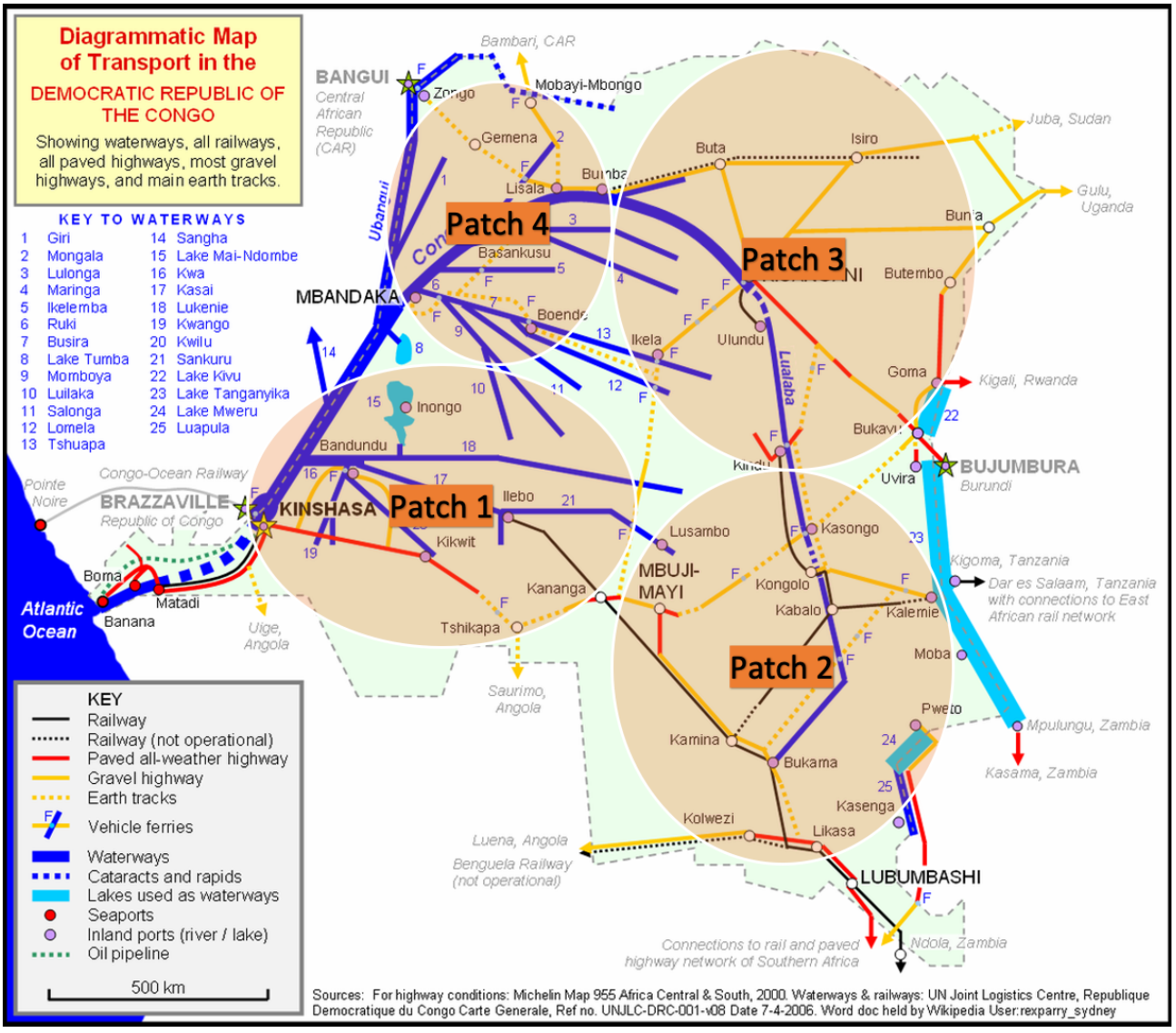

Figure 2: Travel networks in Kinshasa province and proposed patch structure

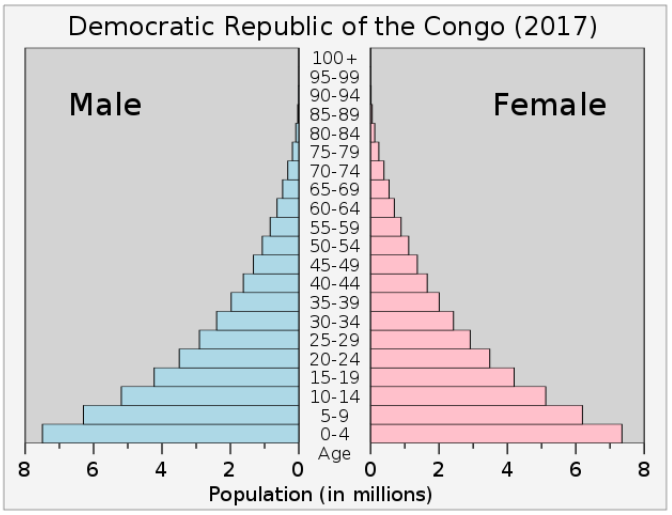

Figure 3: Population pyramid [4]

11.2 Model

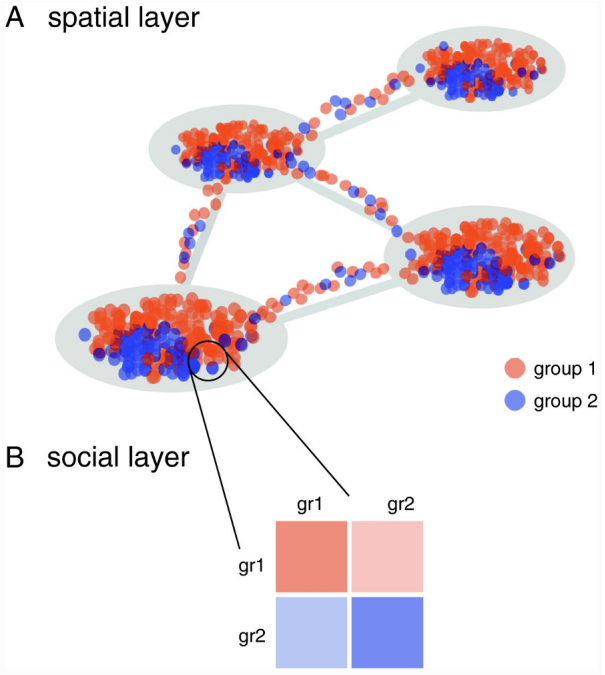

Figure 4: Model scheme as depicted by Appolloni et al. [7]

11.3 Results

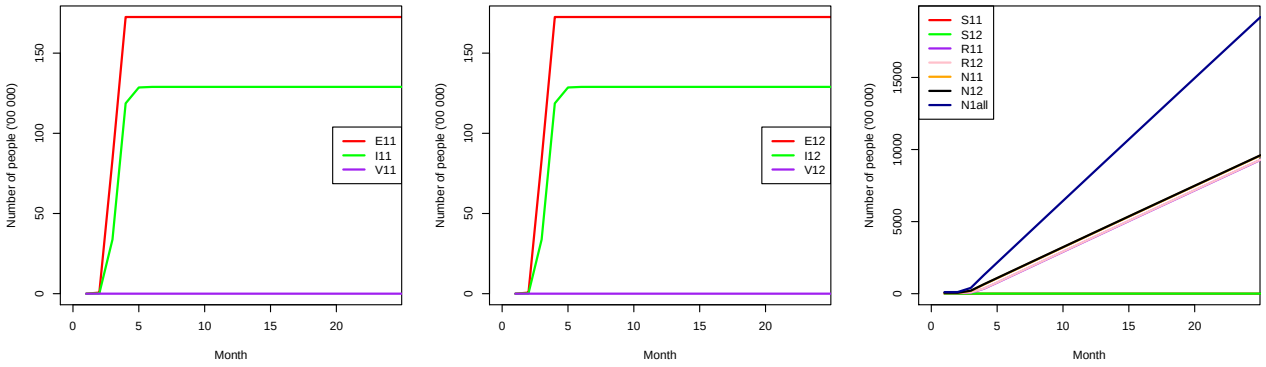

Figure 5: Patch 1 plots

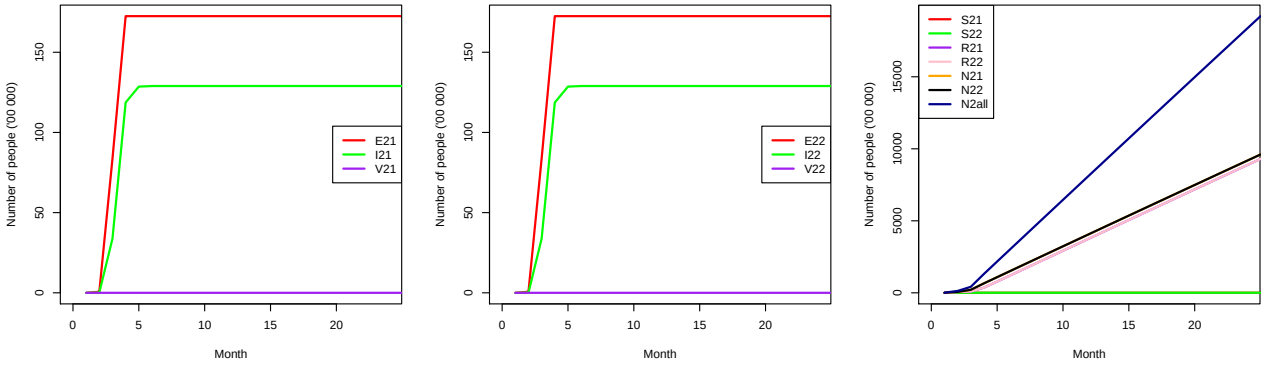

Figure 6: Patch 2 plots

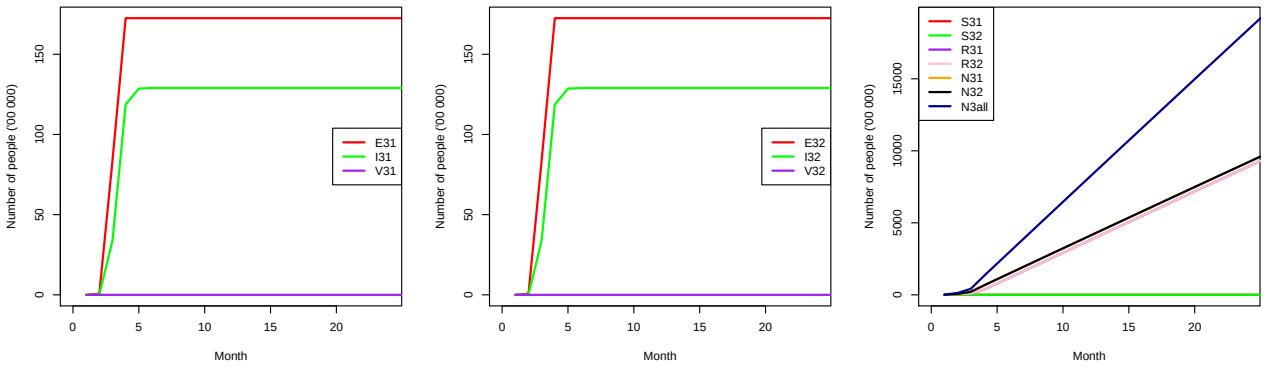

Figure 7: Patch 3 plots

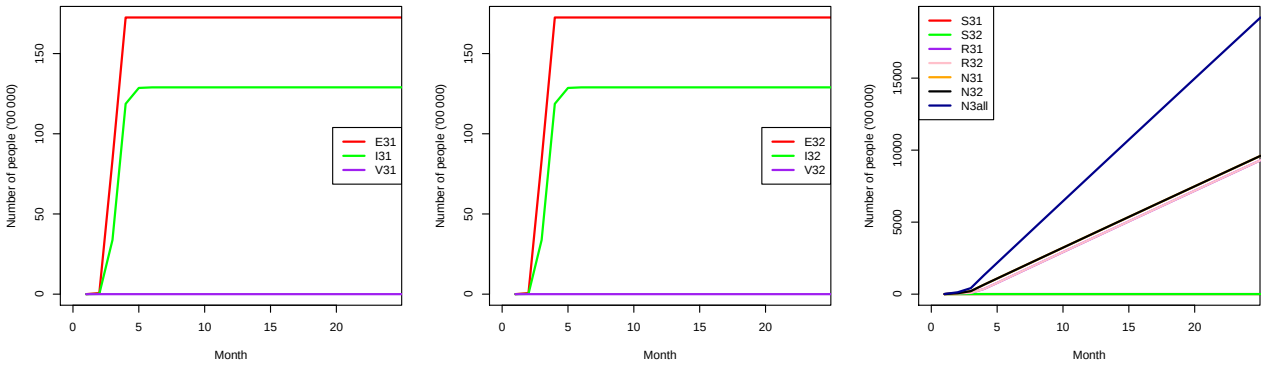

Figure 8: Patch 4 plots

11.4 Sensitivity Analysis

11.4.1 Adjusting β

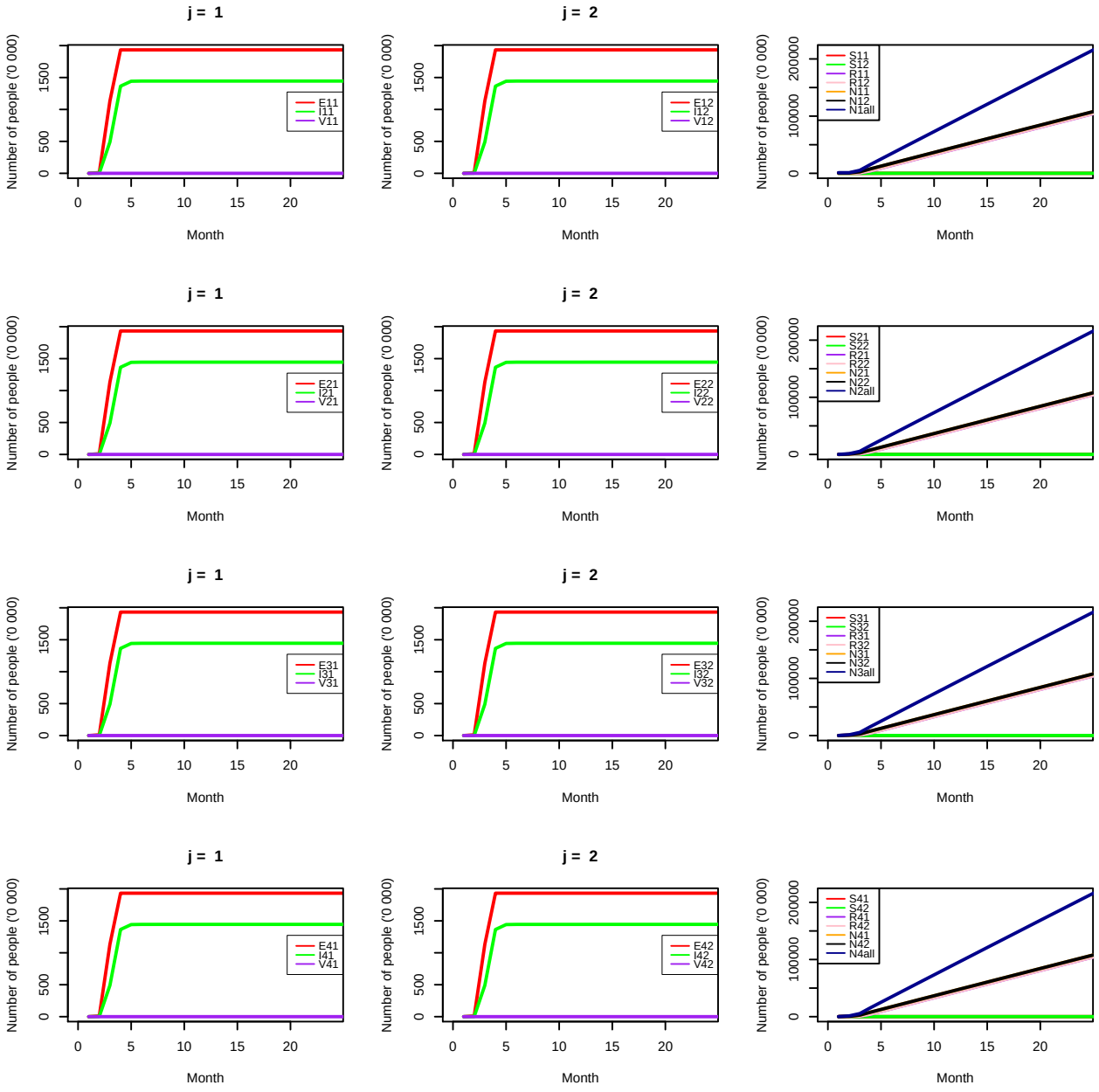

Figure 9: Model output with $\beta = 0.1$

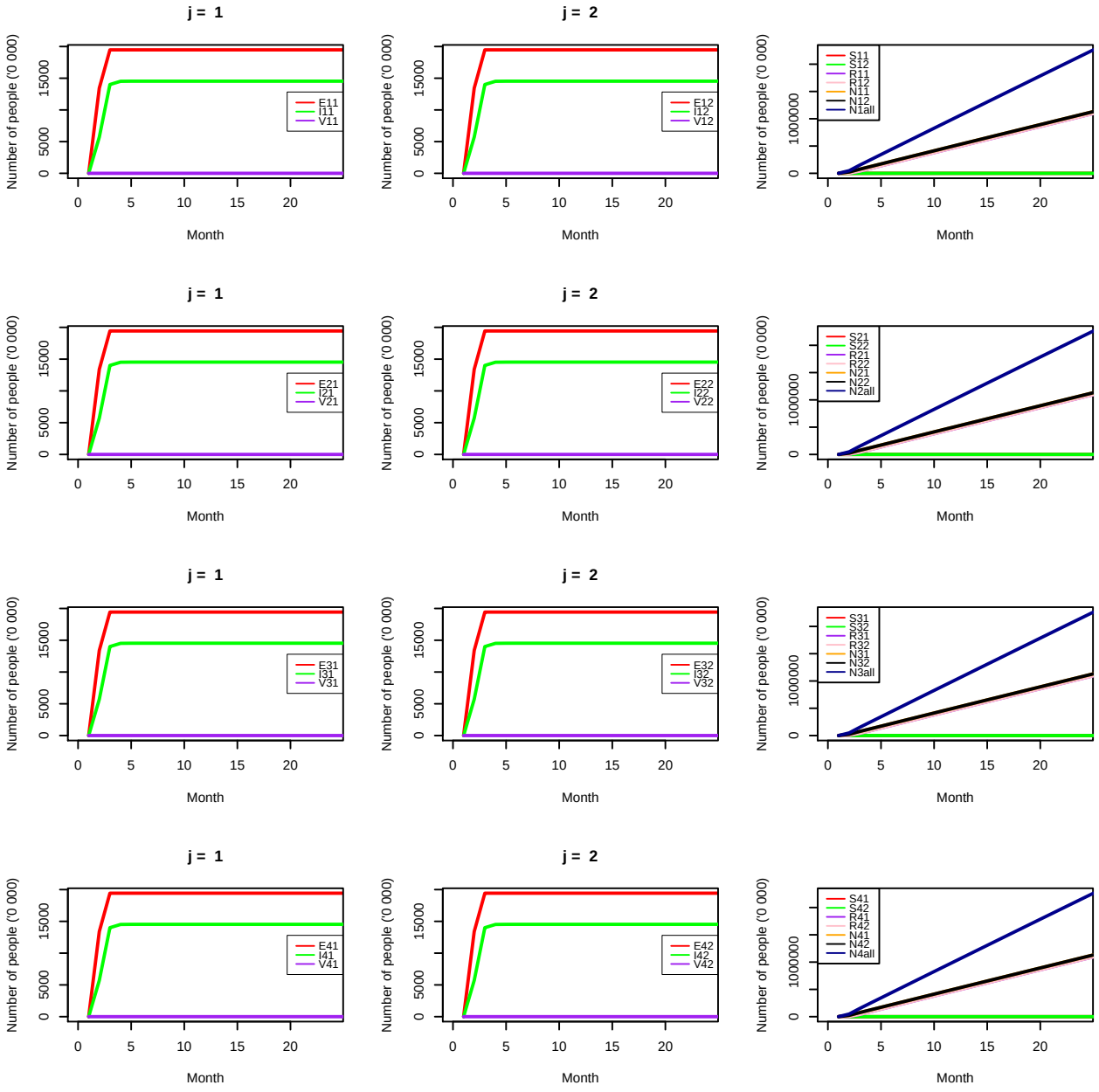

Figure 10: Model output with $\beta = 0.9$

11.4.2 Adjusting γ, ϵ

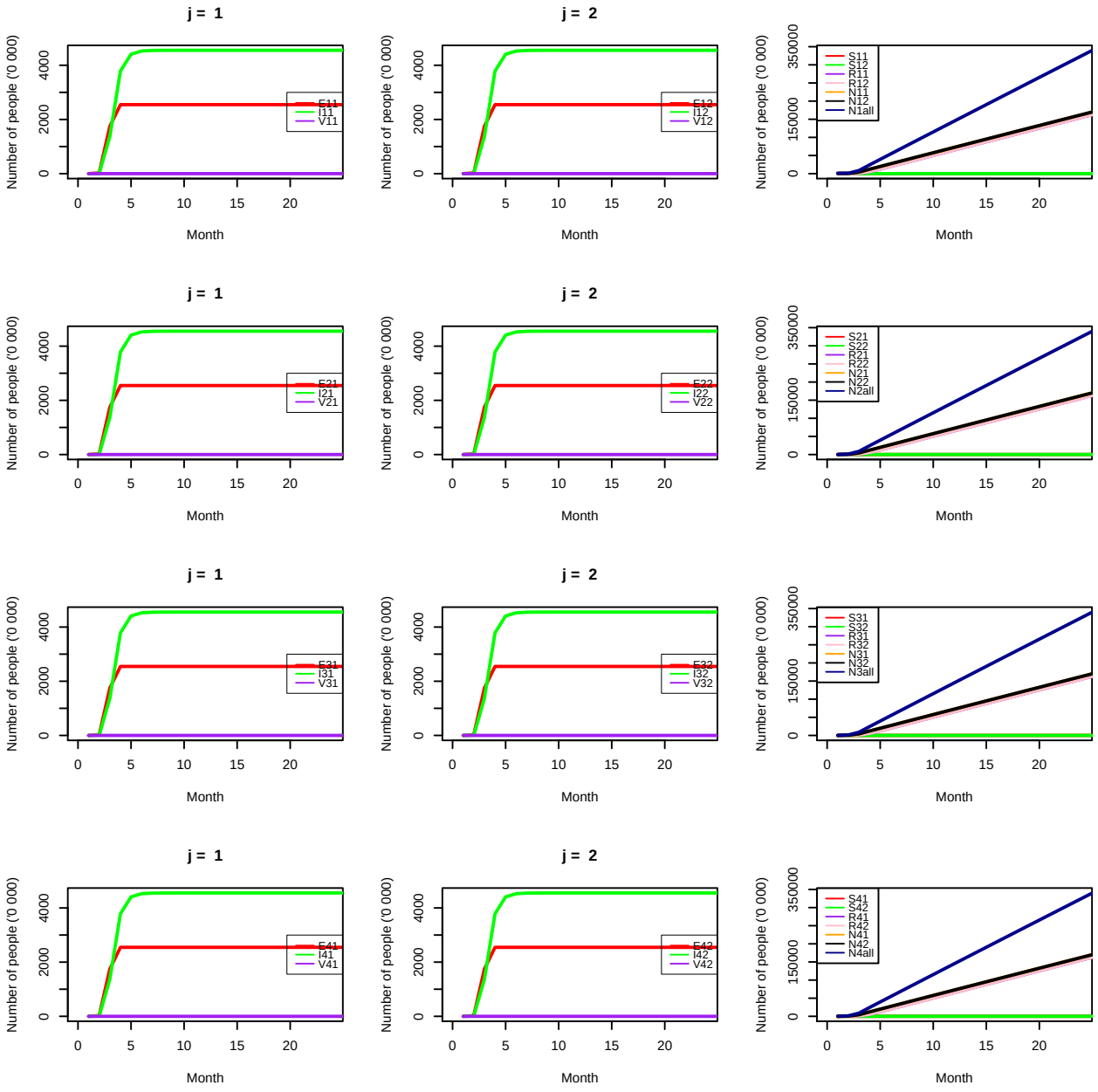

Figure 11: Model output with 10 day incubation period ($\gamma = 1.666667, \epsilon = 3$)

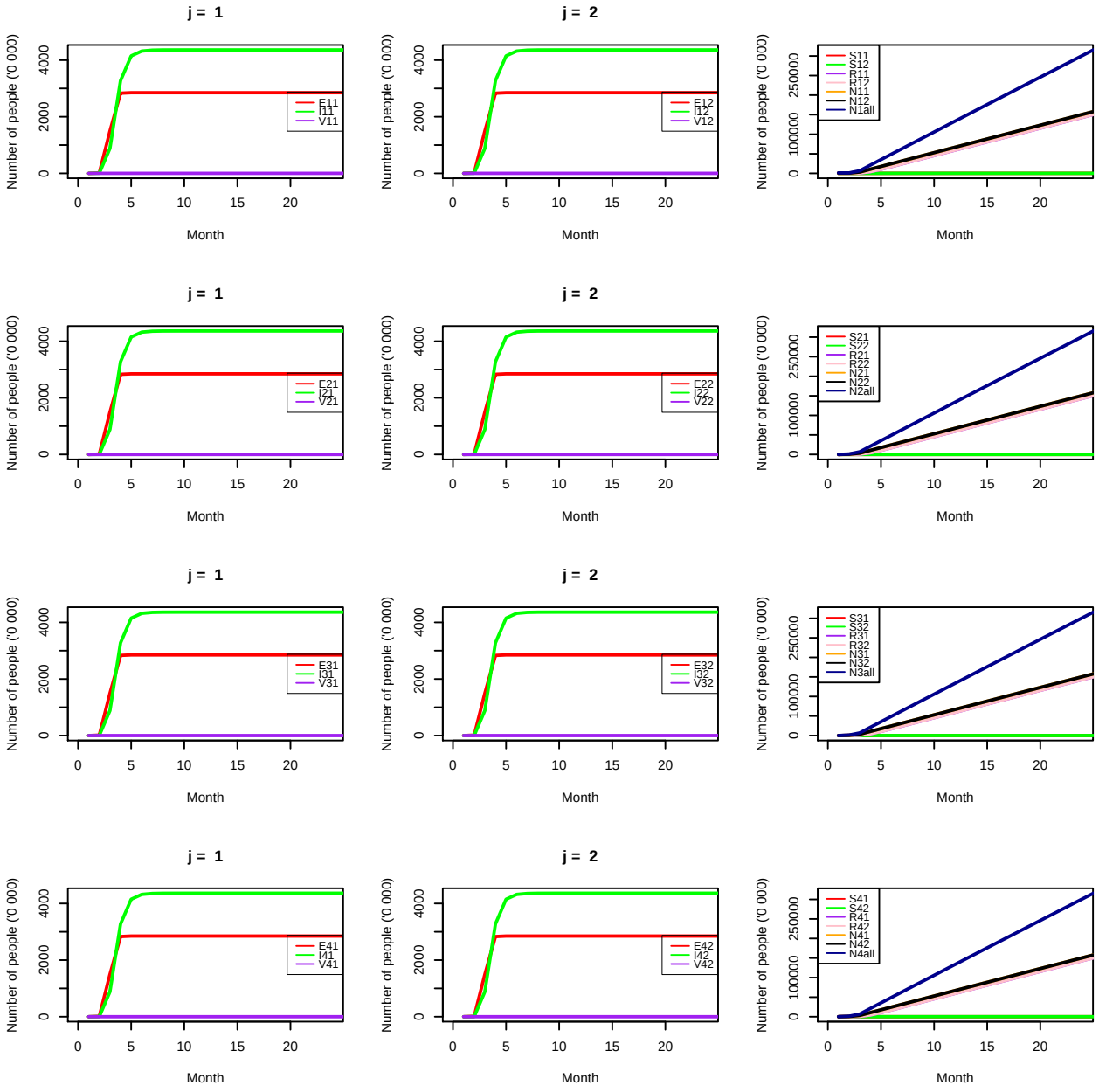

Figure 12: Model output with 12 day incubation period ($\gamma = 1.641791, \epsilon = 2.5$)

11.5 R Code

```
rm(list = ls(all=TRUE))
setwd("~/Documents/Masters 2020:2021/MMID/Ass1")
#####################################
```

```
### data
### to be used in in S V E I R (from WHO, 2019)
# Dec2019
cases <- 3550
#how many in Kinshasa (estimate)
cases <- cases*(14.3/85)
#Vaccination rate - 2008 est
prop.vacc <- 0.92
prop.S <- 1-prop.vacc

### population distribution among patches - randomly allocated
### spatial layer
n.vills <- 3
kinshasa.pop <- 14.3*(10^6) - cases # 2020
capital.pop <- 8.9*(10^6)*(1.0433)^5 # incorporate growth from (2015)

vills.pop <- kinshasa.pop - capital.pop

villages <- rep(0, n.vills)
set.seed(2020)
for (i in 1:vills.pop){
  v <- sample(c(1:n.vills),1)
  villages[v] <- villages[v] + 1
}

pop <- c(capital.pop, villages)
names(pop) <- c("cap", "vill1", "vill2", "vill3")
#proportions belonging to each
props <-pop/sum(pop)

### social layer
# proportion children (0-14 years) - from DRC factbook, CIA
p <- 0.4125
p <- c(p, 1-p)
ps <- matrix(NA, ncol = 4, nrow = 2)
colnames(ps) <- names(pop)
rownames(ps) <- c("children", "adults")
for(j in 1:ncol(ps)){
  for(i in 1:nrow(ps)){
    ps[i,j] <- p[i]*pop[j]
  }
}
ps <- t(ps)
```

```r
# cases matrix
case.m <- ps/sum(ps)*cases

################################
#### Parameters
# birth and rate per month (from crude rate)
mu <- 40.6/(1000*12)
# natural death rate per month (from crude)
alph <- 9.3/(1000*12)
# death due to infection
phi <- 0.125/12 #0.125 per year
# vaccine effectiveness
e <- 0.95
# rate of immunity
kapp <- 0.14286/12 # 0.14286 per year
# beta
b <- 0.09091
# incubation period (rate of infectiousness)
i <- 12
eps <- 1/i *30
# recovery rate
r <- 21-i #days, recovery time
gamm <- 1/r * 30
# vaccination coverage in locality i
etas <- c(rep(0.95, 20))
############################
# social contact matrix
# all locations, Congo
library(readxl)
contmat <- read_excel("MUestimates_all_locations_1.xlsx", sheet = "Congo")
# upper bound of ages (naming cols and rows)
ages <- seq(from = 5, by = 5, length.out = ncol(contmat))
colnames(contmat) <- ages
#rownames(contmat) <- ages
heatmap(as.matrix(contmat), keep.dendro = F)
# set up final social contact matrix
sum11 <- sum(contmat[c(1:2),c(1:2)])
sum22 <- sum(contmat[c(3:16),c(3:16)])
sum12 <- sum(contmat[c(1:2),c(3:16)])
sum21 <- sum(contmat[c(3:16),c(1:2)])
# change to monthly
thetasoc <- 30*matrix(c(sum11, sum12, sum21, sum22), ncol = 2, byrow = T)
colnames(thetasoc) <- c("0-15", "16+")
```

```
rownames(thetasoc) <- colnames(thetasoc)
########################################
#spatial contact matrix - simulated
thetaspa <- diag(rep(1,4))
set.seed(2020)
e <- 30*runif(1)
# all connect to 1 - capital
thetaspa[1, 2:4] <- e
thetaspa[2:4, 1] <- e
# 2 and 3 connected
thetaspa[2,3] <- e
thetaspa[3,2] <- e
# 4 and 3 connected4
thetaspa[4,3] <- e
thetaspa[3,4] <- e
########################################################
#model
patch.i <- function(t, x, parms){
  ###############################

  ######################################
  with(as.list(c(parms, x)),{
    # population of each patch, within each age group
    N11 <- S11+E11+I11+R11+V11
    N12 <- S12+E12+I12+R12+V12

    N21 <- S21+E21+I21+R21+V21
    N22 <- S22+E22+I22+R22+V22

    N31 <- S31+E31+I31+R31+V31
    N32 <- S32+E32+I32+R32+V32

    N41 <- S41+E41+I41+R41+V41
    N42 <- S42+E42+I42+R42+V42

    # proportion which are children
    #pr <- (N11+N21+N31+N41)/(N11+N21+N12+N22+N31+N32+N41+N42)
    # for both age groups
    #pr <- c(pr, 1-pr)

    # divide into components
    N <- matrix(c(N11,N12,N21,N22,N31,N32, N41, N42), ncol = 2, nrow = 4, byrow = T)
    S <- matrix(c(S11,S12,S21,S22,S31,S32, S41, S42), ncol = 2, nrow = 4, byrow = T)
```

```
    V <- matrix(c(V11,V12,V21,V22,V31,V32, V41, V42), ncol = 2, nrow = 4, byrow = T)
    E <- matrix(c(E11,E12,E21,E22,E31,E32, E41, E42), ncol = 2, nrow = 4, byrow = T)
    I <- matrix(c(I11,I12,I21,I22,I31,I32, I41, I42), ncol = 2, nrow = 4, byrow = T)
    R <- matrix(c(R11,R12,R21,R22,R31,R32, R41, R42), ncol = 2, nrow = 4, byrow = T)

    out <- c()
    #mat <- matrix(NA)
    # for each patch i
    for (i in 1:4){
      # for each social group j
      for (j in 1:2){
        #set up indicator var
        for (j in 1:2){
          if(j==1){ind = 1}else{ind=0}
        }

        dS <- ind*mu*(1-eta[i])*N[i,j] - b*I[i,j]*S[i,j]*sum(thetasoc[,j])/N[i,j] + sum(S[,j]*
        dV <- ind*mu*eta[i]*N[i,j] - alph*V[i,j] - kapp*V[i,j] + sum(V[,j]*thetaspa[,i]) - V[i
        dE <- b*I[i,j]*S[i,j]*sum(thetasoc[,j])/N[i,j] - (eps+alph)*E[i,j] + sum(E[,j]*thetasp
        dI <- eps*E[i,j] - (gamm+alph+phi)*I[i,j] + sum(I[,j]*thetaspa[,i]) - I[i,j]*sum(theta
        dR <- gamm*I[i,j] + kapp*V[i,j] - alph*R[i,j] + sum(R[,j]*thetaspa[,i]) - R[i,j]*sum(t

        # order of out: SEIRV (as with start)
        out <- c(out, dS, dE, dI, dR, dV)

        # set negs to zero
        for (k in 1:length(out)){
          if (out[k]>0){}else{out[k]<-0}
        }
      }
    }
    list(out)
  })
}

eta <- rep(0.95, 4)
parms <- c(mu=mu, alph=alph, phi=phi, kapp=kapp, b=b,
           eps=eps, gamm=gamm, eta=eta,
           thetasoc=thetasoc, thetaspa=thetaspa)
# double ratio for children, and patch 1
r <- 1/14
start <- c(S11=prop.S*ps[1,1], E11=0, I11=cases*r*4, R11=prop.vacc*ps[1,1], V11=0,
           S12=prop.S*ps[1,2], E12=0, I12=cases*r, R12=prop.vacc*ps[1,2], V12=0,
```

```
          S21=prop.S*ps[2,1], E21=0, I21=cases*r*2, R21=prop.vacc*ps[2,1], V21=0,
          S22=prop.S*ps[2,2], E22=0, I22=cases*r, R22=prop.vacc*ps[2,2], V22=0,
          S31=prop.S*ps[3,1], E31=0, I31=cases*r*2, R31=prop.vacc*ps[3,1], V31=0,
          S32=prop.S*ps[3,2], E32=0, I32=cases*r, R32=prop.vacc*ps[3,2], V32=0,
          S41=prop.S*ps[4,1], E41=0, I41=cases*r*2, R41=prop.vacc*ps[4,1], V41=0,
          S42=prop.S*ps[4,2], E42=0, I42=cases*r, R42=prop.vacc*ps[4,2], V42=0)
# set seq of times
# monthly for next three years
times <- seq(0, 24, 1)
# solve DE's
library(deSolve)
run <- ode(y = start, times = times, func = patch.i, parms=parms)
# divide into patches
patches <- list(NA, NA, NA, NA)
names(patches) <- c("P1", "P2", "P3", "P4")
for(i in 1:4){
  # for each patch
  res <- matrix(NA, ncol = (ncol(run))/4+1, nrow = nrow(run))
  res[,c(1:11)] <- run[,c(1,c((10*i-8):(10*i+1)))]
  colnames(res) <- rep(NA, 11)
  colnames(res)[c(1:11)] <- colnames(run)[c(1,c((10*i-8):(10*i+1)))]

  # add totals
  Ni <- rowSums(res[,-1])
  Ni1 <- rowSums(res[, c(2:6)])
  Ni2 <- Ni-Ni1
  res <- cbind(res, Ni1, Ni2, Ni)
  colnames(res)[(ncol(res)-2):ncol(res)] <- paste("N", i, c(1,2,"all"), sep="")

  # add to list
  patches[[i]] <- res
}

# plot
cols <- c("red", "green", "purple", "pink",
          "orange", "black", "darkblue", "darkred", "darkgreen")

for (k in 1:4){ #k=patch
  #
  #pdf(file = paste("patch",k,".pdf", sep=""), width = 12, compress = F)
  soln <- patches[[k]]

  # in tens of thousands
```

```
  soln <- soln/(10^4)

  par(mfrow=c(1,3))
  for (i in 1:2){#i=age group
    run <- soln[,c((5*i-3):(5*i+1))][,-c(1,4,5)]
    #
    # plot SEI - others not of interest
    plot(run[,1], type = "l", lwd = 2, col = cols[1],
         ylim=c(0, max(run)), xlim=c(0,24),
         ylab ="Number of people ('0 000)", xlab="Month")
    for (j in 2:(ncol(run))){
      lines(run[,j], col = cols[j], lwd = 2)
    }
    legend("bottomright", legend = colnames(run), col = cols, lwd = 2)

  }

  #plot N's and R
  run <- soln[ ,c(5,10,(ncol(soln)-2):ncol(soln))]
  plot(run[,1], type = "l", lwd = 2, col = cols[1],
       ylim=c(0, max(run)), xlim=c(0,24),
       ylab ="Number of people ('0 000)", xlab="Month")
  for (j in 2:ncol(run)){
    lines(run[,j], col = cols[j], lwd = 2)
  }
  legend("bottomright", legend = colnames(run), col = cols, lwd = 2)
  #dev.off()
}

########################################
# NLP
#matrix(0.95, ncol =4, nrow=1)
runmod <- function(eta){
  #eta = array of 4
  parms <- c(mu=mu, alph=alph, phi=phi, kapp=kapp, b=b,
             eps=eps, gamm=gamm, eta=eta,
             thetasoc=thetasoc, thetaspa=thetaspa)
  run <- ode(y = start, times = times, func = patch.i, parms=parms)

  return(run)
}

#objective function
```

```
eval_f <- function(x){
  Is <- runmod(eta=x)[, c(4,9,14,19,24,29,34,39)]

  return(list("objective" = max(rowSums(Is)), "gradient"=rep(0,4)))
  #
}

set.seed(2020)
x0 <- runif(4)

#lower/upper bounds
lb <- rep(0,4)
ub <- rep(1,4)

# available vaccines
vmax <- 8*(10^5)


#contraints
eval_g_ineq <- function(x){
  constr <- -mu*24*t(as.matrix(pop))%*%as.matrix(x)+vmax

  grad <- c(x[2]+x[3]+x[4],
            x[1]+x[3]+x[4],
            x[1]+x[2]+x[4],
            x[1]+x[2]+x[3])

  return(list("constraints"=constr, "jacobian" = grad))
}
#,

library(nloptr)

#local_opts <- list( "algorithm" = "NLOPT_LD_LBFGS", "xtol_rel"  = 1.0e-7 )
opts <- list( "algorithm" = "NLOPT_LN_COBYLA",
              "xtol_rel"  = 1.0e-2,
              "maxeval"   = 500)
set.seed(2020)
res <- nloptr(x0=x0,
              eval_f=eval_f,
              lb=lb,
              ub=ub,
              eval_g_ineq=eval_g_ineq,
```

```
              opts=opts)

# solutions
eta.opt <- res$solution
names(eta.opt) <- c("Patch 1 (capital city)", paste("Patch", c(2:4), sep=" "))
library(xtable)
t <- as.matrix(eta.opt)
colnames(t) <- c("$eta_i$")
xtable(t(t), digits = 4)
res$objective
res$num_constraints_ineq

############################################################
######## plots from optimal eta
parms <- c(mu=mu, alph=alph, phi=phi, kapp=kapp, b=b,
           eps=eps, gamm=gamm, eta=eta.opt,
           thetasoc=thetasoc, thetaspa=thetaspa)

# double ratio for children, and patch 1
r <- 1/14
start <- c(S11=prop.S*ps[1,1], E11=0, I11=cases*r*4, R11=prop.vacc*ps[1,1], V11=0,
           S12=prop.S*ps[1,2], E12=0, I12=cases*r, R12=prop.vacc*ps[1,2], V12=0,
           S21=prop.S*ps[2,1], E21=0, I21=cases*r*2, R21=prop.vacc*ps[2,1], V21=0,
           S22=prop.S*ps[2,2], E22=0, I22=cases*r, R22=prop.vacc*ps[2,2], V22=0,
           S31=prop.S*ps[3,1], E31=0, I31=cases*r*2, R31=prop.vacc*ps[3,1], V31=0,
           S32=prop.S*ps[3,2], E32=0, I32=cases*r, R32=prop.vacc*ps[3,2], V32=0,
           S41=prop.S*ps[4,1], E41=0, I41=cases*r*2, R41=prop.vacc*ps[4,1], V41=0,
           S42=prop.S*ps[4,2], E42=0, I42=cases*r, R42=prop.vacc*ps[4,2], V42=0)

# set seq of times
# monthly for next two years
times <- seq(0, 24, 1)
# solve DE's
library(deSolve)
sim <- ode(y = start, times = times, func = patch.i, parms=parms)

#######################################
# divide into patches
to.patch <- function(sim){
  patches <- list(NA, NA, NA, NA)
  names(patches) <- c("P1", "P2", "P3", "P4")
  for(i in 1:4){
    # for each patch
```

```
    res <- matrix(NA, ncol = (ncol(sim))/4+1, nrow = nrow(sim))
    res[,c(1:11)] <- sim[,c(1,c((10*i-8):(10*i+1)))]
    colnames(res) <- rep(NA, 11)
    colnames(res)[c(1:11)] <- colnames(sim)[c(1,c((10*i-8):(10*i+1)))]

    # add totals
    Ni <- rowSums(res[,-1])
    Ni1 <- rowSums(res[, c(2:6)])
    Ni2 <- Ni-Ni1
    res <- cbind(res, Ni1, Ni2, Ni)
    colnames(res)[(ncol(res)-2):ncol(res)] <- paste("N", i, c(1,2,"all"), sep="")

    # add to list
    patches[[i]] <- res
  }

  return(patches)
}


# plot
cols <- c("red", "green", "purple", "pink",
          "orange", "black", "darkblue", "darkred", "darkgreen")

plot.patch <- function(soln){
  soln <- soln/(10^4)

  # plot EIRV
  #par(mfrow=c(1,3))
  for (i in 1:2){#i=age group
    run <- soln[,c((5*i-3):(5*i+1))][,-c(1,4)]
    #
    # plot SEI - others not of interest
    plot(run[,1], type = "l", lwd = 2, col = cols[1],
         ylim=c(0, max(run)), xlim=c(0,24),
         ylab ="Number of people ('0 000)", xlab="Month",
         main=paste("j = ", i, sep=" "))
    for (j in 2:(ncol(run))){
      lines(run[,j], col = cols[j], lwd = 2)
    }
    legend("right", legend = colnames(run), col = cols, lwd = 1,
           cex=.75, box.lwd = .5,
           xjust = 0, x.intersp = .5, y.intersp = .75)
```

```
  }

  #plot N's and R
  run <- soln[ ,c(2,7,5,10,(ncol(soln)-2):ncol(soln))]
  plot(run[,1], type = "l", lwd = 2, col = cols[1],
       ylim=c(0, max(run)), xlim=c(0,24),
       ylab ="Number of people ('0 000)", xlab="Month")
  for (j in 2:ncol(run)){
    lines(run[,j], col = cols[j], lwd = 2)
  }
  legend("topleft", legend = colnames(run), col = cols, lwd = 1,
         cex=0.75, xjust = 0, x.intersp = .5, y.intersp = .75)
  #dev.off()
}

for (k in 1:4){ #k=patch
  pdf(file = paste("patch",k,".pdf", sep=""), width = 12, height = 4, compress = F)
  soln <- to.patch(sim)[[k]]

  par(mfrow=c(1,3))
  plot.patch(soln = soln)

  dev.off()
}

##################################
# Sensitivity - b
#function for running ODE's, plotting
run.sim <-function(parms){
  # run
  sim <- ode(y = start, times = times, func = patch.i, parms=parms)

  #plot each patch
  for (k in 1:4){
    plot.patch(soln = to.patch(sim)[[k]])
  }
}

#bseq <- seq(from=0, to=0.9, length.out = 10)
bseq <- c(0.1,0.9)
for (v in 1:length(bseq)){
  # define new parms
```

```
  parms1 <- c(mu=mu, alph=alph, phi=phi, kapp=kapp, b=bseq[v],
              eps=eps, gamm=gamm, eta=eta.opt,
              thetasoc=thetasoc, thetaspa=thetaspa)

  pdf(file = paste("beta",v, ".pdf", sep = ""), compress = F, width = 7)
  #dev.new(width=7, height=6, unit="in")
  par(mfrow=c(4,3), cex=.5)
  run.sim(parms1)
  dev.off()
  Sys.sleep(0.5)
}

##############################
# Sensitivity  - gamm, eps
# incubation period (rate of infectiousness)
iseq <- c(10:12)
epsseq <- rep(0,3)
for(i in 1:length(iseq)){
  epsseq[i] <- 1/iseq[i] *30
}
# recovery rate
rseq <- rep(21,3)-epsseq #days, recovery time
gammseq <- rep(0,3)
for(i in 1:length(gammseq)){
  gammseq[i] <- 1/rseq[i] * 30
}

### plots for each
for (v in 1:length(gammseq)){
  # define new parms
  parms1 <- c(mu=mu, alph=alph, phi=phi, kapp=kapp, b=b,
              eps=epsseq[v], gamm=gammseq[v], eta=eta.opt,
              thetasoc=thetasoc, thetaspa=thetaspa)

  pdf(file = paste("gammeps",v, ".pdf", sep = ""), compress = F, width = 7)
  #dev.new(width=7, height=6, unit="in")
  par(mfrow=c(4,3), cex=.5)
  run.sim(parms1)
  dev.off()
  Sys.sleep(0.5)
}
```