Cost-effectiveness of an increase in hand hygiene on ICU's

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1 ABSTRACT

1.1 Abstract

Hand hygiene is an important measure in preventing hospital-acquired infections (HAI's). These HAI's are life-threatening, especially for immunocompromised patients. An increase in hand hygiene is expected to lower these HAI's significantly. The goal of this research is the creation of a model that simulates the spread of meticillin-resistant Staphylococcus aureus in ICU's, including the effects of hand hygiene compliance. The model shows that an increase in hand hygiene will lower the amount of MRSA infections significantly, but further financial insights should be followed up with further research.

2 INTRODUCTION

2.1 Goal

The aim of this research is to recreate and improve the model described in a paper by Luangasanatip [1]. Assessing the cost-effectiveness of an increase in hand hygiene compliance (HHC) in hospitals. In the research, a model was developed to determine whether reductions in meticillin-resistant Staphylococcus aureus bloodstream infections (MRSA-BSIs) would make hand hygiene interventions cost-effective. To research this subject, a few questions needs to be answered. In the first place is questions about the MRSA-BSI infections need to be asked. These include, "What is the chance to get infected?" and "How does the infection spread?". For the economic side of this research, other question are important. "What are the cost of hand hygiene interventions?" and "What are the costs associated with a MRSA-BSI infection?". These questions overall lead to the main research question, which is: "Is an increase in hand hygiene intervention cost-effective in hospitals?"

2.2 Theory

Hospital-acquired infections (HAI's) are a major cause of morbidity and mortality among hospitalized patients [2]. In Germany, it is estimated that around 20.000 - 30.000 patients die each year due to HAI's [3]. On average, 18.6% of patients in German ICU have acquired an HAI [4]. The single most important measurement to reduce HAI's is the increase of HHC [5], [6]. These HAIs increase the costs of stay due to increase in hospital days and care costs [7]. In Germany the additional costs per patient with MRSA induced pneumonia is €17,282, with the total burden of HAI's in Europe being an estimated €13-24 billion [8]. The difference between these costs is substantial between developed and developing countries, as the risks of infections are 2 to 20 times higher in developing countries [9]. HHC varies between countries. Germany had a mean HHC of 60.9% taken from 700 institutions. Whereas another study in the UK in a single large ICU had a HHC of 43% [10]. Overall, there is a large variance between institutes in the same country, and an even larger variance between Western countries.

Previous studies found that an increase of HHC is cheap, relative to the cost of the HAI's [1].

3 METHODS

3.1 The software model

For the establishment of the model we have used two models. Both of these models where programmed using the R programming language making use of the deSolve package. The code for both of the models can be found in the appendix.

Figure 1: Method process

3.1.1 *Original model.*

The original model used consisted of a recreation from *Cost-effectiveness of interventions to improve hand hygiene in healthcare workers in middle-income hospital settings: a model-based analysis; Luangasanatip et al. (2018).*

The biological model for the original model can be seen in figure 2.

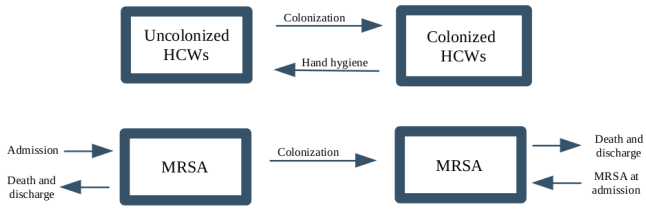

Figure 2: Biological model of the original model
source: *Cost-effectiveness of interventions to improve hand hygiene in healthcare workers in middle-income hospital settings: a model-based analysis; Luangasanatip et al (2018)*

These parameters used to validate the implemented model vs the original model were copied directly from the original paper. These values can be found in the underlying table (note: description of each value can be found in the appendix).

Parameter	Value
U_{pat}	10
C_{pat}	0
N_{pat}	10
U_{hcw}	9
C_{hcw}	0
N_{hcw}	9
μ	0.173
γ	0.173
π	0.087
c	8
P_{hp}	0.0113
P_{ph}	9
c'	9
HHC	0.1
λ	$(HHC * c' * n_{pat})/(1 - HHC) * n_{hcw}$

Table 1: Used parameters for first model

This model was made using the underlying differential equations.

$$\frac{dU_{pat}}{dt} = -\mu * U_{pat} - c * p_{hp} * U_{pat} * \frac{C_{hcw}}{N_{hcw}} + (1-\pi) * (\mu * U_{pat} + \gamma * C_{pat}) \quad (1)$$

$$\frac{dC_{pat}}{dt} = -\gamma * C_{pat} + c * p_{hp} * U_{pat} * \frac{C_{hcw}}{N_{hcw}} + \pi * (\mu * U_{pat} + \gamma * C_{pat}) \quad (2)$$

$$\frac{dU_{hcw}}{dt} = -(c' * P_{ph} * C_{pat} * \frac{U_{hcw}}{N_{hcw}}) + \lambda * C_{hcw} \quad (3)$$

$$\frac{dC_{hcw}}{dt} = (c' * P_{ph} * C_{pat} * \frac{U_{hcw}}{N_{hcw}}) - \lambda * C_{hcw} \quad (4)$$

In **equation 1** the differential equation for calculating the difference in the amount of uncolonised patients is depicted. The $-\mu * U_{pat}$ part of the equation calculates the amount of removed uncolonised patients in the given time frame. $c * P_{hp} * U_{pat} * \frac{C_{hcw}}{N_{hcw}}$ represents the number of patients that get colonized due to interactions between patients and healthcare workers. The last part of the equation is $(1-\pi) * (\mu * U_{pat} + \gamma * C_{pat})$, the $(1-\pi)$ calculates the percentage of uncolonised patients that get admitted to the ICU while $(\mu * U_{pat} + \gamma * C_{pat})$ calculates the total amount of discharged patients. This means that this model always operates under the assumption that every bed in a given ICU is always taken by a patient.

Equation 2 calculates the difference in the amount of colonized patients. Equation 2 uses $c * p_{hp} * U_{pat} * \frac{C_{hcw}}{N_{hcw}}$ to calculate the number of patients that get colonized due to interactions between patients and healthcare workers and $(\mu * U_{pat} + \gamma * C_{pat})$ to calculate the total number of discharges, just like equation 1. Where these formulas differ is in the calculation of removed patients. In equation 2 this is done with $-\gamma * C_{pat}$. Another difference is that equation 2 multiplies the amount of discharges by π instead of $(1-\pi)$, this is because π represent the fraction of the admissions that is colonized, which is the value needed for calculating the change in the number of colonized patients.

Equation 3 is used to calculate the difference in colonized healthcare workers over time. In this formula, $(c' * P_{ph} * C_{pat} * \frac{U_{hcw}}{N_{hcw}})$ stands for the number of healthcare workers that get colonized due to contact with colonized patients. The last part of the formule, $\lambda * C_{hcw}$, is for calculating the number of colonized healthcare workers that get uncolonised as a result of hand hygiene compliance.

The last equation is **equation 4**. This equation is the same as 3, except for the fact that addition and subtraction have swapped places.

3.1.2 *Improved model.*

A secondary model was used. This recreation uses the model described as in *Modeling nosocomial infections of methicillin-resistant Staphylococcus aureus with environment contamination; Wang et al. 2017.* Correct implementation was tested using the parameters as provided by the original paper. The used parameters can be found in the underlying table.

Parameter	**Value**
	Starting state
P_u	10
P_c	13
H_u	17
H_c	6
B_e	1000
	Proportion of colonized patients
o	0.067
N_p	23
N_h	23
αp	0.0435
	Probability of colonization (1/day)
βp	0.72
βh	0.20
	Discharge rate (1/day)
γ_u	0.067
γ_c	0.046
	Cleaning / disinfection (1/day)
γ_b	0.7
	Colonization rate from environment (CFUs/day)
K_p	0.000004
K_h	0.00001
η	0.1
μ_c	1
	Contamination rate to environment (CFUs/day)
V_p	235
V_h	235

Table 2: Parameters used for validation of second model

The improved model is based on the same theory as the original model. The models only big deviation from the improved model

when compared to the original model is the addition of an extra variable for the bacterial load in the environment.

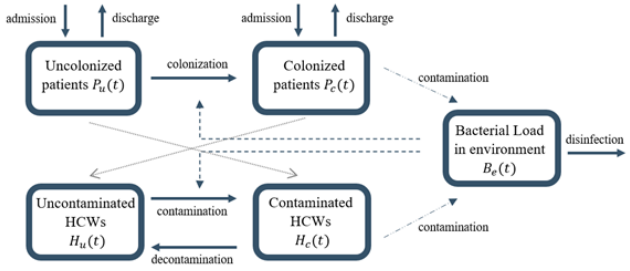

Figure 3: Biological model of the improved model[11]

In figure 3 the biological model of the improved model is depicted. This model made from the following differential equations:

$$\begin{aligned}\frac{dP_u(t)}{dt} &= (1-\theta)[\gamma_u P_u(t) + \gamma_c P_c(t)] \\ &\quad - \alpha_p \beta_p (1-\eta) P_u(t) H_c(t) \\ &\quad - k_p P_u(t) B_e(t) - \gamma_u P_u(t)\end{aligned} \tag{5}$$

$$\begin{aligned}\frac{dP_c(t)}{dt} &= \theta[\gamma_u P_u(t) + \gamma_c P_c(t)] + \alpha_p \beta_p (1-\eta) P_u(t) H_c(t) \\ &\quad + k_p P_u(t) B_c(t) - \gamma_c P_c(t)\end{aligned} \tag{6}$$

$$\begin{aligned}\frac{dH_u(t)}{dt} &= -\alpha_p \beta_h (1-\eta) P_c(t) Hu(t) + \mu_c H_c(t) \\ &\quad - k_h H_u(t) B_e(t)\end{aligned} \tag{7}$$

$$\begin{aligned}\frac{dH_c(t)}{dt} &= \alpha_p \beta_h (1-\eta) P_c(t) Hu(t) - \mu_c H_c(t) \\ &\quad + k_h H_u(t) B_e(t)\end{aligned} \tag{8}$$

$$\frac{dB_c(t)}{dt} = \nu_p P_c(t) + \nu_h H_c(t) - \gamma_b B_e(t) \tag{9}$$

The equation depicted in **equation 5** is used for the calculation of the change in the uncolonised patients variable.$(1-\theta)$ is the portion of admitted patients that are colonized, while $[\gamma_u P_u(t) + \gamma_c P_c(t)]$ is the total number of discharged patients. These values are then multiplied to give the number of admitted uncolonised patients. So the calculation of the admission rate is comparable to the original model when comparing this equation to equation 1. $\alpha_p \beta_p (1-\eta) P_u(t) H_c(t)$ is the formula for calculating the number of patients that transitions from uncolonised to colonized due to contact with a colonized healthcare worker. Lastly the number of patients colonized due to the environment and the number of discharged uncolonised patients are calculated by $k_p P_u(t) B_e(t)$ and $\gamma_u P_u(t)$, respectively.

Equation 6 is similar to equation 5. The biggest differences being that equation 6 uses θ directly, adds the amount of colonized patients due to the environment instead of subtracting it, and calculates the number of discharged colonized patients instead of the number of uncolonised.

Healthcare workers can be colonized in multiple ways. These ways include colonization due to contact with colonized patients and colonization due to the environment. These ways are represented in **equation 7** and 8 by the formulas $\alpha_p \beta_h (1-\eta) P_c(t) Hu(t)$ and $k_h H_u(t) B_e(t)$ respectively. Naturally healthcare workers can also be decolonized, this is show as $\mu_c H_c(t)$ in formulas 7 and 8. Equation 7 is used for calculating the difference in uncolonised healthcare workers and **equation 8** for calculating the change in the colonized healthcare worker variable.

The last variable of this model is the bacterial load in the environment. This variable is dependent on the change in the environmental load due to colonized patients and healthcare workers, and is also dependent on the cleaning and disinfection of the environment. In **equation 9** $\nu_p P_c(t) + \nu_h H_c(t)$ represents environment change due to colonized patients added to the environmental change due to colonized healthcare workers. $\gamma_b B_e(t)$ is the used to calculate the change due to cleaning and desinfection of the environment.

3.1.3 *Evaluation with real world data.*

Currently, both models use non-grouped data. These data points are sourced from different continents/countries, this makes validation cumbersome as there is no comparable data which inhabits proper validation. Using real world data sourced from single sources (e.g. hospitals) with known MRSA transmission rates after an increase in HHC will enable adequate comparisons between model and real world data.

4 RESULTS

In this research, two models are recreated. Both models are dynamic models for evaluating the effectiveness of hand hygiene promotion interventions. In the models, numbers of (un)colonized patients and healthcare workers are plotted against time, with different simulations of hand hygiene compliance.

4.1 The original model

The results of the original model are showed in figure 4. When looking at the model for 10% hand hygiene compliance in figure 4 we can see that the amount of uncolonised healthcare workers slowly decreases from 10 to around 8 in the 20 days time. Taking a look at the number of colonized patients, we can see a slight increase to around 1 colonized patient before reaching equilibrium. This is when the initial states are set to every healthcare worker and patient being uncolonised at t=0. When comparing this to the model with a 40% hand hygiene compliance, some rather small changes can be observed. The most notable of these changes is the change in equilibrium of uncolonised and colonized patients. There seems to be a difference of around 0.5 patients. A particularly interesting observation is that when looking at the difference between 40% hand hygiene compliance and 90% hand hygiene compliance, there seems to be no difference in the model. This is in conflict with literature on the subject, seeing as this increase in hand hygiene should theoretically have a large impact on the amount of colonized patients and healthcare workers. These small changes are probably caused by the fact that there don't seem to be many infections to begin with. This is also in conflict with literature, especially at a hand hygiene compliance of only 10%. This is most likely caused by the value of some parameters not being accurate when compared to real world data.

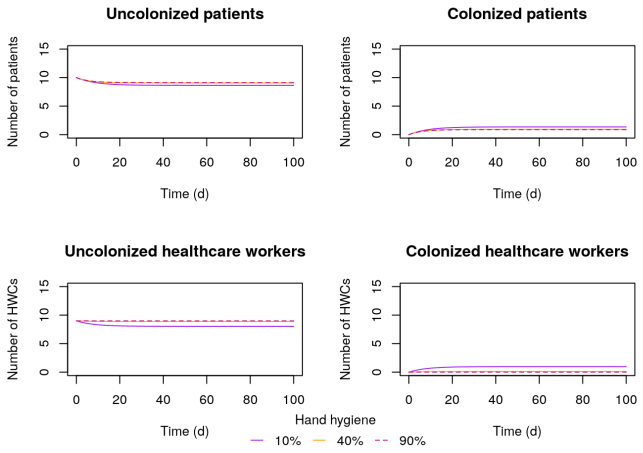

Figure 4: Model 1
top-left: Number of uncolonized patients over time.
top-right: Number of colonized patients over time.
bottom-left: Number of uncolonized HCWs over time.
bottom-left: Number of colonized HCWs over time.

4.2 Improving the original model

Results of the second model, an improving of the original model, can be seen in figure 5. In the model a fast decrease in the number of uncolonized patients is visible for both 10%, 40%, and 90% hand hygiene compliance. The system reaches an equilibrium in the amount of colonized and uncolonized patients around t=30, which means after 30 days the amount of patients that are colonized and uncolonized becomes stable. The equilibrium that is found is at 5 uncolonized and 18 colonized patients for 10% hand hygiene compliance. When comparing this to the system with 40% hand hygiene compliance, we can observe a large difference. The equilibrium in this system is also formed after around 30 days, but it is found at 8 uncolonized patients and 15 colonized patients. This is a considerable difference, as expected when looking at prior literature on the subject. When looking at the number of colonized and uncolonized healthcare workers, we can observe an interesting spike at around t=2, this is equivalent to 2 days. In this tiny spike a large percentage of the healthcare workers becomes uncolonized, but after a few days the model dips down again to reach an equilibrium. This spike and sudden drop can be explained by the rapid increase of the bacterial load in the environment. Because of the rapid increase in the bacterial load in the environment, the amount of colonization amongst the healthcare workers starts to increase, causing the dips after the sharp peak. When observing the system at 90% hand hygiene compliance, it can be observed that there are no more colonized healthcare workers. The only group with colonization is patients. The group of colonized patients slowly starts to decrease to reach an equilibrium at around 6 colonized patients somewhere around t=150, this means after 150 days the equilibrium of the system is reached. An interesting change in the number of bacteria can also be observed. The number of bacteria in the environment increase very rapidly over the first few days, but after that there is a sharp decline. This is caused by a combination of both the decrease in colonized patients and colonized healthcare workers. It can also be observed that even with just a few colonized patients, a lot of the bacteria can still be found in the environment.

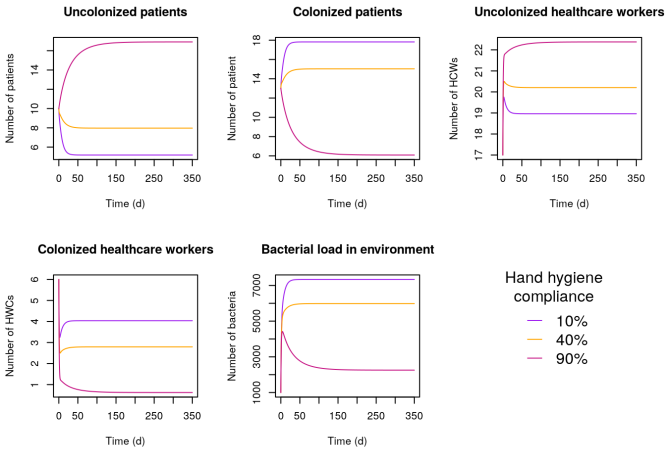

Figure 5: Model 2
top-left: Number of uncolonized patients over time.
top-middle: Number of colonized patients over time.
top-left: Number of uncolonized HCWs over time.
bottom-left: Number of colonized HCWs over time.
bottom-right: Bacterial load in enviroment.

5 DISCUSSION AND CONCLUSION

5.1 Conclusion

To conclude, based on the original model, hand hygiene compliance would probably not be cost-effected. This is because, if the original model is to be believed, hand hygiene compliance would not be an effective measure to reduce the spread of MRSA in ICUs. We believe the model is not correct based on prior literature. This is affirmed by the improved model. We can not conclude that hand hygiene interventions are cost-effective because due to time restrictions we were unable to produce a working economic model. However, based on that there are fewer infections when hand hygiene interventions are increased, it could likely be effective as current treatment of patients with MRSA infections costs around €17000,- per patient. The expected monetary savings could be a subject for a follow-up research. We can however conclude that, based on available literature, the improved model is an actual improvement over the original model.

5.2 Discussion

When comparing the original model to literature and when looking at the results in figure 4 we observed quite a lot of discrepancies. This was largely due to the fact that it seems like hand hygiene had only a small effect, if any, on the transmission dynamic. These findings are inconsistent with literature. The cause of this might lay in the calculation of the lambda parameter. Which looks like it might need to be dynamic instead of static, but when programming this, the results didn't change drastically. Another thing that seem

quite odd is the fact that looking at the results of the original model, we can observe that there are only a few colonized patients and healthcare workers at any given time, even when HHC is set to something very low like 10%. This lead us to conclude that there was either a problem with the chosen parameter values or that it had something to do with the differential equations. A combination of multiple parameter values that have to do with the colonization rate seems to be the most plausible explanation for the low number of colonization's at any given point in time.

The improved model takes more parameters into account and also adds one variable, the bacterial load in the environment. This is a variable that isn't used in the original model, even though it seems to be quite an important one. Because of this variable, we can now also calculate the amount of colonization of patient and healthcare workers based on the amount of MRSA in the environment. This one variable already makes the improved model several times more accurate than the original one.

Something that was changed in the improved model however was the decontamination rate of healthcare workers. This was put to 24 in the original improved model, but because of the formula this is way too high. In the formula $\mu_c * H_c(t)$ is used in both the differential equations for the amount of colonized an uncolonised healthcare workers. However, putting the value of μ_c to 24 would give us a value of 24 * 6 with six contaminated healthcare workers. This seems odd seeing as this value would be 144, which would mean that on that day 144 healthcare workers would be decontaminated. To get around this problem the formula should be changed to $\frac{1}{\mu_c} * H_c(t)$ or μ_c should become a rate like 1/24, which would mean 1 in 24 healthcare workers would be decontaminated per day. Another fix could be setting the decontamination rate to a standard number and not making a constant rate. The solution we used in this study was changing the parameter to $\mu_c = 1$. This would translate to a 100% decolonization rate of healthcare workers. This might seem high, but when looking at the original value of 24, it seems like they meant that 24 healthcare workers get decolonized per day. This is more than the total amount of healthcare workers actually working in the ICU, which means that 100% decolonization would be reasonable. Another problem with this value is that we could not find any sources that might lead to a sensible value for these parameters. We could also not find what theory this parameter seems to be based on.

When trying to validate the model, we ran into a few problems, the biggest of which was the fact that there seem to be no publicly available data sets that could be used to validate the transmission dynamics model. This lead us to having to validate the model using existing literature. This method of evaluation is less reliable and more prone to error, but nevertheless the only way to evaluate the validity of the models. Future research is needed to gather the data necessary to make a good evaluation of the validity of the improved model using real world data.

Explaining the discrepancies between the results of the original model compared to the improved model is a challenging feed. The biggest difference between the models is the introduction of the new variable for bacterial load in the environment. However, the introduction of this variable should not have such a drastic effect on the results, especially seeing as the theory behind both of the models is quite alike, if not exactly the same. This leads us to conclude that the most likely explanation for these discrepancies is in the chosen parameters values, the biggest ones probably being the parameters that make up the colonisation rate in the original model.

5.3 Future research

In the research described by Luangasanatip et al. (2018) [1] the transmission dynamic model is combined with an economic model. As they state, the local information on the resources used for the hand hygiene intervention is limited. Since they used an Australian survey and applying Thai pay-scale salaries, the cost are estimated, which means there could be significant differences between the model and real life. Originally we wanted to redo the complete research. But after the issues we found with the models and the insufficiency's in documentation, we decided to not remake the economic model. A future research in this area could research the actually economic model in which up-to-date costs of hand hygiene intervention and hospital costs are included.

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6 APPENDIX

6.1 Model 1 parameter description

Parameter	Description
U_{pat}	Number of MRSA (−ve) patients on ward at one time
C_{pat}	Number of MRSA (+ve) patients on ward at one time
N_{pat}	Number of beds ($U_{pat} + C_{pat}$)
U_{hcw}	Number of MRSA (−ve) HCWs per shift
C_{hcw}	Number of MRSA (+ve) HCWs per shift
N_{hcw}	Number of total HCWs per shift ($U_{HCW} + C_{HCW}$)
μ	Removal rate of uncolonized patients (1/mean length of stay) (per day)
γ	Removal rate of colonized patients (1/mean length of stay) (per day)
π	Proportion of colonized admission
c	Patient/HCW contact per day (per patient)
P_{hp}	Transmission probability (1/mean length of stay) (per day)
P_{ph}	Transmission probability from patient to HCW per contact
c'	HCW/patient contact per day (per HCW)
HHC	Hand hygiene compliance
λ	Hand hygiene rate defined as: $\frac{HHC*C'*n_{pat}}{(1-HHC)*n_{HCW}}$

Table 3: Parameters used for first model

6.2 Model 2 parameter description

Parameter	Description
	Starting state
P_u	Uncolonized patients
P_c	Colonized patients
H_u	Uncolonized patients
H_c	Colonized patients
B_e	Bacterial load environment (CFUs)
	Proportion of colonized patients
o	Admitted in hospital (1/ day)
N_p	Number of patients
N_h	Number of HCWs
αp	Contact rate (1/day)
	Probability of colonization (1/day)
βp	By colonized patients
βh	By contaminated HCWs
	Discharge rate (1/day)
γ_u	Uncolonized patients
γ_c	Colonized patients
	Cleaning / disinfection (1/day)
γ_b	rate of environment
	Colonization rate from environment (CFUs/day)
K_p	Of uncolonized patients
K_h	Of uncontaminated HCWs
N	Hand hygiene complience
μ_c	Decontamination rate of HCWs (1/day)
	Contamination rate to environment (CFUs/day)
V_p	By colonized patients
V_h	By contaminated HCWs

Table 4: Desc used for second model

6.3 Code

Raw code which is used can be found below, but can also be found on github.com/devalk96/Thema08.

6.3.1 Model 1.

```
library(deSolve)


parameters <- c(npat = 10,
                nhcw = 9,
                u = 0.173,
                y = 0.173,
                pi = 0.087,
                c = 8,
                Php = 0.0113,
                c_a = 9,
                Pph = 9,
                HHC = 0.1,
                lambda = (0.1*9*10)/(1-0.1)*9
                )

state <- c(Upat = 10,
           Cpat = 0,
           Uhcw = 9,
           Chcw = 0)

HandHygene <- function(t, state, parameters) {
  with(as.list(c(state, parameters)),{
    # rate of change
    dUpat <- -u * Upat - (c*Php*Upat*Chcw)/nhcw +
      (1 - pi) * (u*Upat+y*Cpat)

    dCpat <- -y * Cpat + (c*Php*Upat*Chcw)/nhcw +
      pi * (u*Upat + y * Cpat)

    dUhcw <- - (c*Pph*Cpat*Uhcw)/nhcw +
      lambda * Chcw

    dChcw <- (c*Pph*Cpat*Uhcw)/nhcw -
      lambda * Chcw

    # return the rate of change
    list(c(dUpat, dCpat, dUhcw, dChcw))
  })
}

times <- seq(0, 100, by = 0.01)

out <- ode(y = state, times = times,
           func = HandHygene, parms = parameters)

parameters <- c(npat = 10,
                nhcw = 9,
                u = 0.173,
                y = 0.173,
                pi = 0.087,
                c = 8,
                Php = 0.0113,
                c_a = 9,
                Pph = 9,
                HHC = 0.4,
                lambda = (0.4*9*10)/(1-0.4)*9
                )
out2 <- ode(y = state, times = times,
            func = HandHygene, parms = parameters)

parameters["HHC"] <- 0.9
parameters["lambda"] <- (0.9*9*10)/(1-0.9)*9
out3 <- ode(y = state, times = times,
            func = HandHygene, parms = parameters)

plot(out, out2, out3,
     lwd=1,
     lty=c(1,1,2),
     col=c("Purple","Orange", "mediumvioletred"),
     xlab = "Time (d)",
     ylab = c("Number of patients",
              "Number of patients",
              "Number of HWCs",
              "Number of HWCs"),
     main = c("Uncolonized patients",
              "Colonized patients",
              "Uncolonized healthcare workers",
              "Colonized healthcare worker"),
      ylim = list(c(0,15),
                  c(0,15),
                  c(0,15),
                  c(0,15)))

par(fig=c(0,1,0,1), oma= c(0,0,0,0),
    mar = c(0,0,0,0), new=TRUE)

plot(0,0, type='l', bty = 'n', xaxt='n', yaxt = 'n')
legend("bottom", legend=c("10%", "40%", "90%"),
       lty = c(1,1,2),
       col = c("Purple","Orange", "mediumvioletred"),
       title = "Hand hygiene",
       cex = 1.2,
       xpd=TRUE,
       horiz=TRUE,
       bty='n',
       seg.len = 1)
```

6.3.2 *Model 2.*

```r
library(deSolve)

parameters <- c(o = 0.067,
                Np = 23,
                Nh = 23,
                alphap = 0.0435,
                betap = 0.72,
                betah = 0.20,
                Yu = 0.067,
                Yc = 0.046,
                Yb = 0.7,
                Kp = 0.000004,
                Kh = 0.00001,
                N = 0.1,
                Uc = 1,
                Vp = 235,
                Vh = 235
                )

state <- c(Put = 10,
           Pct = 13,
           Hut = 17,
           Hct = 6,
           Bet = 1000)

HandHygene <- function(t, state, parameters) {
  with(as.list(c(state, parameters)),{
    # rate of change
    dPut <- (1-o) * (Yu * Put + Yc * Pct) - alphap *
      betap * (1-N) * Put * Hct - Kp * Put * Bet - Yu
          ↪ * Put

    dPct <- o * (Yu * Put + Yc * Pct) + alphap *
        ↪ betap *
      (1-N) * Put * Hct + Kp * Put * Bet - Yc * Pct

    dHut <- -alphap * betah * (1-N) * Pct * Hut +
      Uc * Hct - Kh * Hut * Bet

    dHct <- alphap * betah * (1-N) * Pct * Hut -
      Uc * Hct + Kh * Hut * Bet

    dBet <- Vp*Pct + Vh * Hct - Yb * Bet

    # return the rate of change
    list(c(dPut, dPct, dHut, dHct, dBet))
  })
}

times <- seq(0, 350, by = 0.01)

out <-
  ode(
    y = state,
    times = times,
    func = HandHygene,
    parms = parameters
  )
parameters["N"] <- 0.4
out2 <-
  ode(
    y = state,
    times = times,
    func = HandHygene,
    parms = parameters
  )
parameters["N"] <- 0.9
out3 <-
  ode(
    y = state,
    times = times,
    func = HandHygene,
    parms = parameters
  )
par(mgp = c(3, 1, 0))
plot(
  out,
  out2,
  out3,
  lwd = 1,
  lty = 1,
  col = c("Purple", "Orange", "mediumvioletred"),
  xlab = "Time␣(d)",
  ylab = c(
    "Number␣of␣patients",
    "Number␣of␣patient",
    "Number␣of␣HCWs",
    "Number␣of␣HWCs",
    "Number␣of␣bacteria"
  ),
  main = c(
    "Uncolonized␣patients",
    "Colonized␣patients",
    "Uncolonized␣healthcare␣workers",
    "Colonized␣healthcare␣worker",
    "Bacterial␣load␣in␣environment"
  )
)

par(
  fig = c(0, 1, 0, 1),
```

```
    oma = c(0, 0, 0, 0),
    mar = c(0, 0, 0, 0),
    new = TRUE
  )
  plot(
    0,
    0,
    type = 'l',
    bty = 'n',
    xaxt = 'n',
    yaxt = 'n'
  )
  coord <- par("usr")

  legend(
    x = coord[2] * 0.5,
    y = coord[4] * -0.25,
    legend = c("10%", "40%", "90%"),
    box.lty = 1,
    lty = 1,
    col = c("Purple", "Orange", "mediumvioletred"),
    title = "Hand hygiene\ncompliance",
    cex = 1.7,
    xpd = TRUE,
    bty = 'n',
    seg.len = 1
  )
```