Supplementary Appendix to:
Resistance Risks of Cholera Prophylaxis for United Nations Peacekeepers

Amber Kunkel, Joseph A. Lewnard, Virginia E. Pitzer, Ted Cohen

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1. Parameter calculations

This section further details the methods used to choose values or ranges for some parameters.

Relative transmissibility of asymptomatic infections

Values used for this parameter in various models have ranged from essentially 0 to 100%, reflecting continued uncertainty about the role of asymptomatic infections in cholera transmission (1, 2). Our baseline value of 10% is consistent with that used in (3). Lewnard et al. assumed an 8.58 times increase in stool volume among symptomatic cases relative to asymptomatic (4-6); assuming a linear relationship between stool volume and infectiousness, this would result in a similar value of 11.7%. Because other models have assumed different values, and it is not clear that the relationship between stool volume and infectiousness is in fact linear, we also test values of 50% and 1% in sensitivity analyses below.

Probability of resistance acquisition

We chose to include a wide range for this parameter, recognizing the lack of data on its value.

The upper bound of 1% reflects the frequency of clinical relapses seen in (7) and continued vibrio excretion in (8). Though few if any of these cases were attributable to acquired resistance, we considered them to at least provide an upper bound on the probability of acquiring resistance.

The lower bound of 1 in 100,000 was chosen to reflect the observation that acquired resistance has repeatedly and rapidly appeared in the presence of widespread
antibiotic pressure (9, 10), demonstrating the possibility of acquired resistance emerging during an epidemic of this size.

**Probability of treatment given symptoms**

Antibiotic treatment is recommended by the WHO only in cases of severe cholera (11). To estimate a reasonable range for this parameter, we looked at the percentage of symptomatic cholera cases hospitalized, classified as severe, or given antibiotics for a number of papers (12-17). These values ranged from 3% (13) to 71% (15) of symptomatic cases being hospitalized or classed as severe, with most estimates ranging from approximately 5-50%.

**Cholera incidence in country of origin**

The primary resource for our chosen range of this parameter was Ali et al (18), which estimates incidence rates by WHO region ranging from 0.1 to 4 per 1,000 (excluding Haiti and the Dominican Republic). For this paper, we increased the upper range to 8 per 1,000, reflecting potential underreporting or country-level variation not captured in this analysis. We set a lower bound of 0.5 per 1,000, assuming peacekeepers from countries with cholera incidence below that point would be unlikely to receive chemoprophylaxis.

2. Sensitivity analysis - baseline calculation

We ran sensitivity analyses for the effects of vaccination, the infectiousness of asymptomatic cases, and the susceptible population size based on 1,000 random parameter sets each repeated until 2,000 importation events had occurred. To facilitate ease of comparison for our sensitivity analyses, we also re-ran our code under our baseline assumptions using only 1,000 random parameter sets (as opposed to 10,000 for the main analysis).

3. Sensitivity analysis - susceptible population size

Figures S1.1 and S1.2 compare the results from our baseline analysis, assuming a susceptible population size of 1,000,000, and a sensitivity analysis assuming a susceptible population size of only 10,000. The results are mostly very similar between these two scenarios, though the excess number of DR infections both overall and conditional on importation are scaled for the smaller population size.
Figure S1.1 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis under the baseline assumption of a susceptible population size of 1,000,000. Blue indicates results favoring prophylaxis and red indicated results favoring no prophylaxis. Similar to Figure 2 in the main text, subplot interpretations are as follows: A) Prophylaxis may increase or decrease the overall expected number of DR cholera infections; these values cluster around zero and never reach $\geq 2000$ (\geq 0.2\% of the population). B) Prophylaxis always decreases the probability of cholera importation. C) Prophylaxis always increases the expected number of DR cholera infections conditional on cholera importation. D) Prophylaxis is likely to prevent $\geq 10$ DS cholera infections per excess DR cholera infection.
Figure S1.2 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis under an assumption of a susceptible population size of 10,000. Results were calculated using the same initial random seed as Figure S1.1. The primary results of our model hold for an assumed population size of 10,000 (compared to the baseline scenario of 1,000,000).

For Figures S1.3 and S1.4, we compared the expected number of individuals receiving antibiotics for prophylaxis or treatment under the prophylaxis and no prophylaxis scenarios. These results were obtained by multiplying the average number of infected individuals under the prophylaxis and no prophylaxis scenarios for each parameter set by the symptom probability and probability of treatment given symptoms to obtain the average number of individuals receiving antibiotic treatment under each scenario. We then took the difference between the prophylaxis and no prophylaxis scenarios and added 500 for the number of peacekeepers receiving antibiotic prophylaxis.

Under our initial population size of one million susceptible individuals (Figure S1.3), prophylaxis in some cases reduces the expected number of individuals who would receive antibiotics by preventing the occurrence of large DS epidemics. When we assume a susceptible population of only 10,000, however, prophylaxis always increases the expected number of individuals receiving antibiotics, as it would still be provided to the same number of peacekeepers but prevent fewer infections in the host population.
Figure S1.3 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis on the approximate number of individuals who receive antibiotics as prophylaxis or treatment under the baseline assumption of a susceptible population size of 1,000,000. Results are based on 500 peacekeepers arriving to a susceptible host population. Blue indicates results favoring prophylaxis and red indicated results favoring no prophylaxis. Prophylaxis may either increase or decrease the expected number of individuals who receive antibiotics.

Figure S1.4 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis on the approximate number of individuals who receive antibiotics as prophylaxis or treatment under an assumption of a susceptible population size of 10,000. In contrast to figure S1.3, prophylaxis always increases the expected number of individuals who receive antibiotics for a susceptible population of size 10,000. Results for the total number of antibiotic doses received are highly dependent on the assumed size of the host population relative to the number of peacekeepers deployed.
4. Sensitivity analysis - effects of vaccination

At baseline, we assumed that all peacekeepers received OCV, and that vaccination resulted in a 65% decrease in the probability of being symptomatic (19) as well as a 63% decrease in the transmissibility of asymptomatic carriers. To derive this second assumption, we used the ratio of mean peak number of V. cholerae organisms per gram of stool from (20) assuming a log-linear relationship between vibrio density and infectiousness, i.e.

\[
\text{infectiousness ratio} = \frac{1}{1 + \log_{10}\left(\frac{1}{\text{vibrio ratio}}\right)}
\]

\[
0.37 = \frac{1}{1 + \log_{10}\left(\frac{1}{9.9 \times 10^5/5.1 \times 10^7}\right)}
\]

As sensitivity analyses, we tested two alternate scenarios. First, we assessed the impact of chemoprophylaxis if peacekeepers were not to receive vaccination. Second, we explored an assumption of a linear relationship between V. cholerae density and infectiousness, i.e. that vaccinated individuals with asymptomatic infection were only \(9.9 \times 10^5/5.1 \times 10^7\)=0.0194 times as infectious as unvaccinated individuals with asymptomatic infection. This second scenario is described as the “greater efficacy of vaccination” scenario below.

Figures S1.5-S1.7 show the effects of these three different vaccination assumptions on the excess number of DR infections, excess importation probability, excess number of DR infections conditional on importation, and ratio of DS infections prevented per excess DR case. The no vaccination assumption increases the expected number of DR cases prevented or caused by prophylaxis and the excess probability of importation resulting from prophylaxis. In contrast, the greater efficacy of vaccination assumption makes importation less likely, and thus decreases the impact of prophylaxis on DR cholera cases as well as the probability of importation. The distributions of DS infections prevented per excess DR case look relatively similar across the three scenarios.
Figure S1.5 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis under the baseline vaccination assumption of a log-linear relationship between vibrio output and infectiousness (repeat of Fig S1.1).

Fig S1.6 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis assuming a linear relationship between vibrio output and infectiousness (i.e. greater efficacy of vaccination).
Fig S1.7 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis under the assumption that all peacekeepers remained unvaccinated.

Figures S1.8-S1.10 show the impact of these vaccination assumptions on the excess number of individuals receiving antibiotics as treatment or prophylaxis under prophylaxis scenario. In our baseline scenario, providing chemoprophylaxis to peacekeepers could either increase or decrease the expected number of individuals receiving antibiotics, depending on the particular parameter set. Under the assumption of greater vaccine efficacy, prophylaxis always increases the expected number of people receiving antibiotics. The no vaccination assumption more frequently results in prophylaxis reducing the expected antibiotic burden.
Figure S1.8 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis on the approximate number of individuals who receive antibiotics as prophylaxis or treatment under the baseline vaccination assumption of a log-linear relationship between vibrio output and infectiousness (repeat of Fig S1.3).

Figure S1.9 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis on the approximate number of individuals who receive antibiotics as prophylaxis or treatment assuming a linear relationship between vibrio output and infectiousness (i.e. assuming greater efficacy of vaccination).
Figure S1.10 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis on the approximate number of individuals who receive antibiotics as prophylaxis or treatment under the assumption that all peacekeepers remained unvaccinated.

In summary, many of the metrics explored in this paper, most notably the ratio of DS cases prevented per excess DR case resulting from prophylaxis, remain similar regardless of the vaccination assumptions used. If vaccination is assumed to be highly effective, the risk of prophylaxis resulting in excess DR cases is lower, but so are its potential benefits in terms of preventing importation and acquired DR cases as well as preventing antibiotic use resulting from a potential epidemic. The potential benefits of this use of antibiotics as chemoprophylaxis is therefore more unclear under this assumption. However, the assumption that vaccinated individuals with asymptomatic infections are <2% as infectious as unvaccinated asymptomatic individuals seems unlikely. Infected individuals who had received OCV in a challenge trial (20) shed \textit{V. cholerae} at, on average, 0.019 times the density observed among infected individuals in the trial who had received a placebo. This provides a lower bound on the expected reduction in infectiousness among asymptomatic infections only, since it reflects both a reduction in shedding density among asymptotically infected individuals receiving vaccine, as well as the prevention of symptomatic infections (associated with higher levels of shedding) among a proportion of vaccine recipients. Furthermore, experimental infection data for most enteric pathogens suggests that the probability of infection varies log-linearly, rather than linearly, with the infectious dose (21). If vaccination were to be less effective against transmission than our baseline scenario, we may instead see results resembling those from the “no vaccination” scenario shown here, in which the potential benefits of prophylaxis were even more clear than at baseline.

5. Sensitivity analysis - infectiousness of asymptomatic cases

At baseline, we assumed that asymptomatic cases were 10% as infectious as symptomatic ones, as described above. Figures S1.11-S1.16 compare those baseline...
results with those obtained assuming that asymptomatic cases were either 1% or 50% as infectious as symptomatic cases.

When we assume a greater difference in infectiousness between symptomatic and asymptomatic cases, there are fewer importation events overall and thus prophylaxis has a smaller impact on the probability of importation and number of DR infections than when we assume a more similar infectiousness of symptomatic and asymptomatic infections. However, we still expect prophylaxis to prevent a similar number of DS infections per excess DR infection. Because there are fewer importations when we assume asymptomatic cases are less infectious, we also predict the excess number of individuals receiving antibiotics to be highest under this scenario. The opposite is true when we assume a smaller difference in infectiousness between symptomatic and asymptomatic cases; then, we see a larger impact of prophylaxis on the probability of importation and number of DR infections, and prophylaxis more frequently decreases the expected number of individuals receiving antibiotics. Again, we expect prophylaxis to prevent a similar number of DS infections per excess DR infection.

![Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis under the baseline assumption that asymptomatic individuals are 10% as infectious as symptomatic individuals (repeat of Fig S1.1).](image)

Figure S1.11 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis under the baseline assumption that asymptomatic individuals are 10% as infectious as symptomatic individuals (repeat of Fig S1.1).
Figure S1.12 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis under the assumption that asymptomatic individuals are 1% as infectious as symptomatic individuals.

Figure S1.13 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis under the assumption that asymptomatic individuals are 50% as infectious as symptomatic individuals.
Figure S1.14 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis on the approximate number of individuals who receive antibiotics as prophylaxis or treatment under the baseline assumption that asymptomatic individuals are 10% as infectious as symptomatic individuals (repeat of Fig S1.3).

Figure S1.15 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis on the approximate number of individuals who receive antibiotics as prophylaxis or treatment under the assumption that asymptomatic individuals are 1% as infectious as symptomatic individuals.
Figure S1.16 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis on the approximate number of individuals who receive antibiotics as prophylaxis or treatment under the assumption that asymptomatic individuals are 50% as infectious as symptomatic individuals.

6. Sensitivity analysis - effects of prophylaxis

At baseline, we assumed that individuals receiving prophylaxis were 0.34 times as likely to be infected by a DS strain as individuals not receiving prophylaxis, based on a systematic review of the reduction in the rate of at least one positive sample during follow-up among contacts receiving prophylaxis (22). For this sensitivity analysis, we varied this number to 0.18 (“higher prophylaxis efficacy”) and 0.66 (“lower prophylaxis efficacy”), based on the 95% confidence interval from the same review. As in the main analysis, we assumed that individuals receiving prophylaxis who became infected had a shorter average duration of infection than those not receiving prophylaxis (2.26 days, as opposed to 5 days). These results are shown in Figures S1.17-S1.22.

These plots show that, given other parameters are fixed, the results are not very sensitive to the assumed efficacy of prophylaxis, in terms of reduction in infection risk. This low sensitivity likely occurs because prophylaxis is still assumed to be equally effective in terms of reducing duration of infectiousness of individuals receiving prophylaxis if infected. Differences in the results are most apparent in subplot C (Figures S1.17-S1.19), the excess number of DR infections given importation. When prophylaxis efficacy is low, more DS importation events occur, leading to a lower number of excess DR infections given importation. As a result, the importation probability (subplot B) also increases, though this effect is less visible in the figures. Because the probability of importation is low, changing this parameter has only a minor impact on the number of excess DR infections associated with prophylaxis and the number of DS infections prevented per excess DR infection. The risk of infection on prophylaxis also has only minor impact on the number of individuals receiving antibiotics, though prophylaxis appears slightly
more likely to reduce the overall burden of antibiotic use when it is assumed to have greater efficacy.

Figure S1.17 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis under the baseline assumption that the risk ratio of infection on prophylaxis is 0.34 (repeat of Fig S1.1).

Figure S1.18 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis under the assumption that the risk ratio of infection on prophylaxis is 0.18 (higher efficacy of prophylaxis).
Figure S1.19 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis under the assumption that the risk ratio of infection on prophylaxis is 0.66 (lower efficacy of prophylaxis).

Figure S1.20 Simulation mean effects of peacekeeper prophylaxis vs. no prophylaxis on the approximate number of individuals who receive antibiotics as prophylaxis or under the baseline assumption that the risk ratio of infection on prophylaxis is 0.34 (repeat of Fig S1.3).
**7. Sensitivity analysis - impact of variable parameters**

In addition to testing the impact of our assumptions about population size, vaccine efficacy, and asymptomatic transmission on the overall results of our model, we also tested the impact of these assumptions on the contribution of our individual variable parameters on the results (measured as partial rank correlation coefficients, PRCCs).
Figure S1.17 shows PRCCs between the excess number of DR infections resulting from prophylaxis and our six variable parameters (cholera incidence in the peacekeepers’ country of origin, proportion of cholera cases with drug resistance in the peacekeepers’ country of origin, basic reproductive number \(R_0\) in the absence of treatment, symptom probability, probability of treatment given symptoms, and probability of acquired resistance given treatment or prophylaxis) for each of the sensitivity analysis scenarios described above. Our baseline results here are based on the full 10,000 parameter sets reported in the main text. In general, the impacts of these six parameters do not change dramatically between scenarios. The primary exception is the incidence of cholera in the peacekeepers’ country of origin, which has consistently small effects, but the direction of these effects change depending on the particular scenario. Increased incidence tends to be associated with an increase in excess DR cases resulting from prophylaxis for scenarios with higher transmission (i.e. no vaccination, greater asymptomatic transmission) and with a decrease for scenarios with less transmission (i.e. more effective vaccination, less asymptomatic transmission). One possible explanation is that in greater transmission scenarios, it is possible that both DR and DS infections would arrive simultaneously, in which case the DS infection could help block transmission of the DR infection throughout the population via competition. The impact of \(R_0\) also seems to increase with increased transmission, perhaps reflecting a similar mechanism.

Fig S1.23 Partial rank correlation coefficients between variable parameters and the excess number of DR infections resulting from prophylaxis. Figure displays point estimates and 95% confidence intervals. The six variable parameters are as shown in Table 1 of the main text (j: cholera incidence in peacekeeper country of origin, \(R_0\): proportion of DR cholera in the country of origin, \(R_0\): basic reproductive number in the absence of treatment, \(\sigma\): proportion of cholera infections that are symptomatic, \(\tau_{\text{prop}}\): proportion of symptomatic individuals who receive treatment, and \(a_{\text{prop}}\):
The proportion of individuals receiving treatment or prophylaxis who acquire resistance.

Figure S1.18 shows PRCCs between the excess number of DS infections prevented per excess DR infection resulting from prophylaxis and our six variable parameters (cholera incidence in the peacekeepers’ country of origin, proportion of cholera cases with drug resistance in the peacekeepers’ country of origin, basic reproductive number in the absence of treatment, symptom probability, probability of treatment given symptoms, and probability of acquired resistance given treatment or prophylaxis) for each of the sensitivity analysis scenarios described above. Our baseline results here are again based on the full 10,000 parameter sets reported in the main text. These results show even less variation in the impacts of these six parameters between scenarios than the results for the excess number of DR infections.

Fig S1.24 Partial rank correlation coefficients between variable parameters and the number of DS infections prevented per excess DR infection resulting from prophylaxis. Figure displays point estimates and 95% confidence intervals. The six variable parameters are as shown in Table 1 of the main text (j: cholera incidence in peacekeeper country of origin, \( r_R \): proportion of DR cholera in the country of origin, \( R_0 \): basic reproductive number in the absence of treatment, \( \sigma \): proportion of cholera infections that are symptomatic, \( \tau_{\text{prop}} \): proportion of symptomatic individuals who receive treatment, \( a_{\text{prop}} \): proportion of individuals receiving treatment or prophylaxis who acquire resistance).
8. References


# Code used to simulate model from
# Risk-benefit profile of cholera prophylaxis for United Nations peacekeepers
# Written by A. Kunkel

# This code shows the output from a single run.
# It was used to produce Fig 2. It takes only a few minutes.

library(lhs)
library(adaptivetau)
library(parallel)
library(scales)
library(ggplot2)
library(epiR)
library(harvestr)

# Setting up to call the model function
################################
#
# Seed to reproduce parameter sets
# set.seed(1)
#
# Setting fixed parameters
# all parameters are set to their median values
pars_vec = list(
    gamma = 1/5,  # recovery/death symptomatic untreated
    gamma_abx = 1/(5.0-2.74),  # recovery/death DS symptomatic treated
    gamma_a = 1/5,  # recovery/death asymptomatic untreated (same as symptomatic treated)
    beta_am = 0.1,  # multiplier to beta for asymptomatic
    beta_tm = 1,  # multiplier to beta for treated
    N = 1e6,  # population size - host country
    N_imp = 500,  # battalion size
    delta = 1/1.55,  # incubation period
    sigma_vaxm = 1-0.65,  #multiplier probability of symptoms if vaccinated (1 if no vaccination, 1-.65 otherwise)
    beta_vaxm = 0.37,  # multiplier transmissibility asymptomatic infections given vaccination (1 if no vaccination, 0.37 log, 0.0194 linear)
    v_abx = 0.34,  # risk ratio of infection on prophylaxis
    j = (8+.1)/1000/2,
    a_prop = 10^-3.5,
    R0 = (5+1.25)/2,
    tau_prop = (.5+.05)/2,
    dr_prev = .25,
    sigma = 0.255
)

pars_vec = unlist(pars_vec)

# Number of parameter sets to draw
num_iter=1

# Setting up a matrix of parameter draws
# Rows: parameter set draws
# Columns: parameters
pars = as.data.frame(matrix(1, ncol=length(pars_vec), nrow=num_iter))
colnames(pars) <- names(pars_vec)
pars <- as.data.frame(t(t(pars)*pars_vec))

# For each parameter set, do 1 iteration with prophylaxis and 1 without
pars$proph <- T
pars2 <- pars
pars2$proph <- F
pars <- rbind(pars, pars2)

# updating dependent parameters
pars$tau <- pars$tau_prop/(1-pars$tau_prop)*pars$gamma  # rate starting treatment
pars$a <- pars$a_prop/(1-pars$a_prop)*pars$gamma_abx  # rate acquiring resistance
pars$beta <- pars$R0/pars$N/(pars$sigma*1/pars$gamma + (1-pars$sigma)*pars$beta_am/
pars$gamma_a)  # transmission parameter (from symptomatic, not on treatment)
pars$beta_a <- pars$beta_am*pars$beta  # transmission parameter from asymptomatic
pars$beta_t <- pars$beta_tm*pars$beta  # transmission parameter from (effectively) treated

# prevalence incubation-phase asymptomatic among departures - no (effective) prophylaxis
E_a = with(pars, {j*(1-sigma_vaxm*sigma)/sigma*(1/delta)/(365.25)})
# prevalence infectious asymptomatic among departures - no (effective) prophylaxis
I_a = with(pars, {j*(1-sigma_vaxm*sigma)/sigma*(1/gamma_a)/(365.25)})
# prevalence incubation-phase asymptomatic among departures - on (effective) prophylaxis
E_a_abx = with(pars, {v_abx*j*(1-sigma_vaxm*sigma)/sigma*(1/delta)/(365.25)})
# prevalence infectious asymptomatic among departures - on (effective) prophylaxis
I_a_abx = with(pars, {v_abx*j*(1-sigma_vaxm*sigma)/sigma*(1/gamma_abx)/(365.25)})

# Probability of infection at departure by resistance pattern and prophylaxis use
# assume acquired resistant cases still experience decreased infection risk,
# but same duration as if resistant
pars$p_ds = (E_a+I_a)*(1-pars$dr_prev)
pars$p_dr = (E_a+I_a)*(pars$dr_prev)
pars$p_ds_abx = (E_a_abx+I_a_abx)*(1-pars$dr_prev)*(1-pars$a_prop)
pars$p_dr_abx = with(pars, {(E_a+I_a)*dr_prev + v_abx*(E_a+I_a)*(1-dr_prev)*a_prop})

# Run for ... importation events per parameter set
reps = 5000

############################
# PROPHYLAXIS SCENARIO
############################
pars_full <- pars
pars <- pars_full[1,]

# setting up plots
p1 <- ggplot() + xlim(0,125) + ylab('DS Infections (Prophylaxis)') + xlab('Day') +
theme_bw() + ggtitle('C') + scale_y_continuous(labels=comma, limits=c(-50,350000))

p2 <- ggplot() + xlim(0,125) + ylab('DR Infections (Prophylaxis)') + xlab('Day') +
theme_bw() + ggtitle('F') + scale_y_continuous(labels=comma, limits=c(-50,350000))

# counting how many times we have nonzero DS and total
# infections in the presence/absence of prophylaxis
nonzero_proph = 0
nonzero_noproph = 0
nonzero_ds_noproph = 0
nonzero_ds_proph = 0
num_zeros = 0

# for each model repeition
for (iter in 1:reps) {

  print(iter)

  N = pars$N

  # Draw number of DR and DS cases at departure
  # Probabilities depend on whether prophylaxis is applied
  if (pars$proph == F) {
    rand_vals = with(pars,{rmultinom(1,N_imp,c(p_ds,p_dr,1-p_ds-p_dr))})
  } else if (pars$proph == T) {
    rand_vals = with(pars,{rmultinom(1,N_imp,c(p_ds_abx,p_dr_abx,1-p_ds_abx-p_dr_abx))})
  }

  # If no cases at departure, skip to next iteration
  if (rand_vals[3] == pars$N_imp) {
    num_zeros = num_zeros + 1
    next
  }

  # only track asymptomatic infections at departure
  # (assume rest would be detected and isolated)
  Isa_1 = rand_vals[1]
  Ira_1 = rand_vals[2]

  # Determine size of 2nd generation of infected peacekeepers
  # ignore depletion of susceptibles
  # Assume if acquired resistance, all transmission is DR

  # Transmission from peacekeepers infected at departure
  # Assume all peacekeepers still experiencing effects of prophylaxis
  R_0_a_abx <- with(pars,{v_abx*beta_a*beta_vaxm*N/gamma_abx})
  R_0_a <- with(pars,{beta_a*beta_vaxm*N/gamma_a})

  # Second generation
  if (pars$proph==T) {
    # Draw number DS secondary cases
    Is_2_tmp = sum(rpois(n=Isa_1,lambda=R_0_a_abx))
  } else {
## Determine number symptomatic

\( \text{Is}_2 = \text{rbinom}(n=1, size=\text{Is}_2\text{tmp}, p=\text{pars}\sigma_{\text{vaxm}}\times\text{pars}\sigma) \)

\( \text{Is}_a_2 = \text{Is}_2\text{tmp} - \text{Is}_2 \)

## Determine number who acquire resistance

\( \text{Ira}_2\text{acq} = \text{rbinom}(n=1, size=\text{Is}_a_2, p=\text{pars}\text{a}\_prop) \)

\( \text{Ir}_2\text{acq} = \text{rbinom}(n=1, size=\text{Is}_2, p=\text{pars}\text{a}\_prop) \)

\( \text{Is}_2 = \text{Is}_2\text{tmp} - \text{Is}_2 \)

\( \text{Ira}_2\text{acq} = 0 \)

\( \text{Ir}_2\text{acq} = 0 \)

## Draw number DR secondary cases

\( \text{Ir}_2\text{tmp} = \text{sum(rpois}(n=\text{Ira}_1, \lambda=\text{R}\_0\_a)) \)

## Determine number symptomatic

\( \text{Ir}_2 = \text{rbinom}(n=1, size=\text{Ir}_2\text{tmp}, p=\text{pars}\sigma_{\text{vaxm}}\times\text{pars}\sigma) \)

\( \text{Ira}_2 = \text{Ir}_2\text{tmp} - \text{Ir}_2 \)

# Supplement with acquired resistant cases

\( \text{Ira}_2 = \text{Ira}_2 + \text{Ira}_2\text{acq} \)

\( \text{Ir}_2 = \text{Ir}_2 + \text{Ir}_2\text{acq} \)

## If no cases in 2nd generation, skip to next iteration

# (No importation)

\( \text{if} (\text{Ir}_2 == 0 \&\& \text{Ira}_2 == 0 \&\& \text{Is}_2 == 0 \&\& \text{Is}_a_2 == 0 ) \{ \)

\( \text{num_zeros} = \text{num_zeros} + 1 \)

\( \text{next} \)

\}

## Initial conditions

\( \text{init.values} = \text{c(} \)

\( \text{S} = \text{N}, \) # DS, symptomatic, not on treatment

\( \text{Is} = \text{Is}_2, \) # DS, symptomatic, on treatment

\( \text{Ts} = 0, \) # DS, asymptomatic, on treatment

\( \text{Ir} = \text{Ir}_2, \) # DR, symptomatic

\( \text{Isa} = 0, \) # DS, asymptomatic

\( \text{Ira} = 0, \) # DR, asymptomatic

\( \text{Rr} = 0, \) # DR, ever infected

\( \text{Rs} = 0, \) # DS, ever infected (excluding acquired resistance)

\( \text{Isa}_p = \text{Is}_a_2, \) # asymptomatic peacekeepers DS

\( \text{Ira}_p = \text{Ira}_2 \) # asymptomatic peacekeepers DR

\)
\[ p = \frac{\beta_a}{\beta_t} \]

\[ \beta_a = 1000 \]

\[ \text{if} \, \text{no importation} \]

\[ \text{if} \, \text{no cases in the general population, skip to next iteration} \]

\[ \text{sens inf} \]

\[ \text{res inf} \]

\[ \text{results} \]

\[ \text{tf} = \text{final time} = 1000 \]

\[ \text{results} = \text{as.data.frame(ssa.adaptivetau(init.values, transitions, RateF, pars, tf=1000))} \]

\[ \text{res inf} \]

\[ \text{sens inf} \]

\[ \text{if} \, (\text{res inf}==0 \, \&\& \, \text{sens inf}==0) \]
# Counting whether we have at least 1 case (total, and DS)
nonzero_proph = nonzero_proph+1
if (sens_inf > 0) {
    nonzero_ds_proph = nonzero_ds_proph+1
}

# Plot DS and DR infections
p1 = p1 + geom_path(data=results, aes(x=time, y=Is+Isa))
p2 = p2 + geom_path(data=results, aes(x=time, y=Ir+Ira))
}

# END for

# NO PROPHYLAXIS
pars <- pars_full[2,]

# Setting up plots - DS and DR infections on linear and log scales
p3 <- ggplot() + xlim(0,125) + ylab('DS Infections (No Prophylaxis)') + xlab('Day') + theme_bw() + ggtitle('A') + scale_y_continuous(labels=comma, limits=c(-50,350000))
p4 <- ggplot() + xlim(0,125) + ylab('DR Infections (No Prophylaxis)') + xlab('Day') + theme_bw() + ggtitle('D') + scale_y_continuous(labels=comma, limits=c(-50,350000))
p5 <- ggplot() + xlim(0,125) + ylab('DS Infections (No Prophylaxis)') + xlab('Day') + theme_bw() + scale_y_log10(labels=comma) + ggtitle('B')
p6 <- ggplot() + xlim(0,125) + ylab('DR Infections (No Prophylaxis)') + xlab('Day') + theme_bw() + scale_y_log10(labels=comma) + ggtitle('E')

for (iter in 1:reps) {
    print(iter)
    N = pars$N
    # Draw number of DR and DS cases at departure
    # Probabilities depend on whether prophylaxis is applied
    if (pars$proph == F) {
        rand_vals = with(pars,rmultinom(1,N_imp,c(p_ds,p_dr,1-p_ds-p_dr)))
    } else if (pars$proph == T) {
        rand_vals = with(pars,rmultinom(1,N_imp,c(p_ds_abx,p_dr_abx,1-p_ds_abx-p_dr_abx)))
    }
    # If no cases at departure, skip to next iteration
    if (rand_vals[3] == pars$N_imp) {
        #num_zeros = num_zeros + 1
        next
    }
    # only track asymptomatic infections at departure
    # (assume rest would be detected and isolated)
Isa_1 = rand_vals[1]
Ira_1 = rand_vals[2]

# Determine size of 2nd generation of infected peacekeepers
# ignore depletion of susceptibles
# Assume if acquired resistance, all transmission is DR

# Transmission from peacekeepers infected at departure
# Assume all peacekeepers still experiencing effects of prophylaxis
R_0_a_abx <- with(pars, {v_abx * beta_a * beta_vaxm * N / gamma_abx})
R_0_a <- with(pars, {beta_a * beta_vaxm * N / gamma_a})

# Second generation
if (pars$proph == T) {
  # Draw number DS secondary cases
  Is_2_tmp = sum(rpois(n = Isa_1, lambda = R_0_a_abx))
  # Determine number symptomatic
  Is_2 = rbinom(n = 1, size = Is_2_tmp, p = pars$sigma_vaxm * pars$sigma)
  Isa_2 = Is_2_tmp - Is_2
  # Determine number who acquire resistance
  Ira_2_acq = rbinom(n = 1, size = Isa_2, p = pars$a_prop)
  Ir_2_acq = rbinom(n = 1, size = Is_2, p = pars$a_prop)
  Isa_2 = Isa_2 - Ira_2_acq
  Is_2 = Is_2 - Ir_2_acq
} else {
  # As above, but no acquired resistance
  Is_2_tmp = sum(rpois(n = Isa_1, lambda = R_0_a))
  Is_2 = rbinom(n = 1, size = Is_2_tmp, p = pars$sigma_vaxm * pars$sigma)
  Isa_2 = Is_2_tmp - Is_2
  Ira_2_acq = 0
  Ir_2_acq = 0
}

# Draw number DR secondary cases
Ir_2_tmp = sum(rpois(n = Ira_1, lambda = R_0_a))
# Determine number symptomatic
Ir_2 = rbinom(n = 1, size = Ir_2_tmp, p = pars$sigma_vaxm * pars$sigma)
Ira_2 = Ir_2_tmp - Ir_2
# Supplement with acquired resistant cases
Ira_2 = Ira_2 + Ira_2_acq
Ir_2 = Ir_2 + Ir_2_acq

# If no cases in 2nd generation, skip to next iteration
# (No importation)
if (Ir_2 == 0 & Ira_2 == 0 & Is_2 == 0 & Isa_2 == 0) {
  #num_zeros = num_zeros + 1
  next
}

# Initial conditions
init.values = c(
  S = N,
\[
\begin{align*}
\text{Is} &= \text{Is}_2, \quad \text{# DS, symptomatic, not on treatment} \\
\text{Ts} &= 0, \quad \text{# DS, symptomatic, on treatment} \\
\text{Ir} &= \text{Ir}_2, \quad \text{# DR, symptomatic} \\
\text{Isa} &= 0, \quad \text{# DS, asymptomatic} \\
\text{Ira} &= 0, \quad \text{# DR, asymptomatic} \\
\text{Rr} &= 0, \quad \text{# DR, ever infected} \\
\text{Rs} &= 0, \quad \text{# DS, ever infected (excluding acquired resistance)} \\
\text{Ira}_p &= \text{Ira}_2, \quad \text{# asymptomatic peacekeepers DS} \\
\text{Ira}_p &= \text{Ira}_2 \quad \text{# asymptomatic peacekeepers DR} \\
\end{align*}
\]

# Model transitions
transitions = list(
    c(S = -1, Is = +1), # infection (DS, becomes symptomatic)
    c(S = -1, Ir = +1), # infection (DR, becomes symptomatic)
    c(S = -1, Isa = +1), # infection (DS, becomes asymptomatic)
    c(S = -1, Ira = +1), # infection (DR, becomes asymptomatic)
    c(Is = -1, Ts = +1), # starting treatment (DS)
    c(Ts = -1, Ir = +1), # acquiring resistance on treatment
    c(Is = -1, Rs = +1), # death/recovery DS symptomatic untreated
    c(Ir = -1, Rs = +1), # death/recovery DR symptomatic untreated
    c(Ts = -1, Rs = +1), # death/recovery DS symptomatic treated
    c(Isa = -1, Rs = +1), # death/recovery DS asymptomatic untreated
    c(Ira = -1, Rs = +1), # death/recovery DR asymptomatic untreated
    c(Isa_p = -1, Rs = +1), # death/recovery asymptomatic peacekeepers DS
    c(Ira_p = -1, Rs = +1) # death/recovery asymptomatic peacekeepers DR
)

# Rates transitions occur
RateF <- function(x, p, t) {
    return(c(
        p$sigma * (p$beta_a * x$"S" * x$"Is" + p$beta_a * x$"S" * x$"Ia") +
        p$beta_t * x$"S" * x$"Ts" + p$beta_a * p$beta_vaxm * x$"S" * x$"Ira_p"), # DS infection symptomatic
        p$sigma * (p$beta_a * x$"S" * x$"Ir" + p$beta_a * x$"S" * x$"Ia") +
        p$beta_a * p$beta_vaxm * x$"S" * x$"Ira_p"), # DR infection symptomatic
        (1 - p$sigma) * (p$beta_a * x$"S" * x$"Is" + p$beta_a * x$"S" * x$"Ia") +
        p$beta_a * p$beta_vaxm * x$"S" * x$"Ira_p"), # DS infection asymptomatic
        (1 - p$sigma) * (p$beta_a * x$"S" * x$"Ir" + p$beta_a * x$"S" * x$"Ia") +
        p$beta_a * p$beta_vaxm * x$"S" * x$"Ira_p"), # DR infection symptomatic
        p$tau * x$"Is"), # starting treatment (DS)
        p$a * x$"Ts"), # acquiring resistance on treatment
        p$gamma * x$"Is"), # death/recovery DS symptomatic untreated
        p$gamma * x$"Ir"), # death/recovery DR symptomatic untreated
        p$gamma * x$"Ts"), # death/recovery DS symptomatic treated
        p$gamma * x$"Ia"), # death/recovery DS asymptomatic
        p$gamma * x$"Ia"), # death/recovery DR asymptomatic
        p$gamma * x$"Ira_p"), # death/recovery DS asymptomatic peacekeepers
        p$gamma * x$"Ira_p")) # death/recovery DR asymptomatic peacekeepers
    ))
# running the model
# tf = final time = 1000
results = as.data.frame(ssa.adaptivetau(init.values, transitions, RateF, pars, tf=1000))

# subtract initial cases among peacekeepers
res_inf <- results$Rr[length(results$Rr)] - Ir_2 - Ira_2
sens_inf <- results$Rs[length(results$Rs)] - Is_2 - Isa_2

# if no cases in the general population, skip to next iteration
# (no importation)
if (res_inf==0 & sens_inf==0) {
  num_zeros = num_zeros + 1
  next
}

# counting nonzero instances (total and DS)
nonzero_noproph = nonzero_noproph+1
if (sens_inf > 0) {
  nonzero_ds_noproph = nonzero_ds_noproph+1
}

p3 = p3 + geom_path(data=results,aes(x=time,y=Is+Isa))
p4 = p4 + geom_path(data=results,aes(x=time,y=Ir+Ira))
p5 = p5 + geom_path(data=results,aes(x=time,y=Is+Isa))
p6 = p6 + geom_path(data=results,aes(x=time,y=Ir+Ira))

} # END for

# view the output plots
p1
#p2
#p3
#p4
#p5
#p6

######################################################################
############################## END CODE ###############################
######################################################################
# Code used to simulate model from
# Risk-benefit profile of cholera prophylaxis for United Nations peacekeepers
# Written by A. Kunkel

# Note: with 10,000 parameter sets (at baseline) and 2000 runs each, this code
# takes 8 days to run split across 32 threads

# This code produces the results from Fig 3 and, with modification, the Appendix
# figures

library(lhs)
library(adaptivetau)
library(parallel)
library(scales)
library(ggplot2)  # to reproduce same histogram bins, use versions 1.0.0-2.0.0
library(epiR)
library(harvestr)
library(sensitivity)

# Takes a random seed and single parameter set
# Returns: Total # DS cases for next importation event
#          Total # DR cases for next importation event
#          Number of no-importation simulations prior to importation event
cholera_res_model <- function(s, pars) {

  set.seed(s, "L'Ecuyer-CMRG")

  nonzero_ind = F  # is there an importation?
  num_zeros = 0    # number non-importations prior to next importation event

  while (nonzero_ind == F) {

    N = pars$N

    # Draw number of DR and DS cases at departure

    # Probabilities depend on whether prophylaxis is applied
    if (pars$proph == F) {
      rand_vals = with(pars,{rmultinom(1,N_imp,c(p_ds,p_dr,1-p_ds-p_dr))})
    } else if (pars$proph == T) {
      rand_vals = with(pars,{rmultinom(1,N_imp,c(p_ds_abx,p_dr_abx,1-p_ds_abx-p_dr_abx))})
    }

    # If no cases at departure, skip to next iteration
    if (rand_vals[3] == pars$N_imp) {
      num_zeros = num_zeros + 1
      next
    }

    # only track asymptomatic infections at departure
    # (assume rest would be detected and isolated)
    Isa_1 = rand_vals[1]
    Ira_1 = rand_vals[2]
# Determine size of 2nd generation of infected peacekeepers
# ignore depletion of susceptibles
# Assume if acquired resistance, all transmission is DR

# Transmission from peacekeepers infected at departure
# Assume all peacekeepers still experiencing effects of prophylaxis
R_0_a_abx <- with(pars, {v_abx*beta_a*beta_vaxm*N/gamma_abx})
R_0_a <- with(pars, {beta_a*beta_vaxm*N/gamma_a})

# Second generation
if (pars$proph==1) {
  # Draw number DS secondary cases
  Is_2_tmp = sum(rpois(n=Isa_1, lambda=R_0_a_abx))
  # Determine number symptomatic
  Is_2 = rbinom(n=1, size=Is_2_tmp, p=pars$sigma_vaxm*pars$sigma)
  Isa_2 = Is_2_tmp - Is_2
  # Determine number who acquire resistance
  Ira_2_acq = rbinom(n=1, size=Ira_1, p=pars$a_prop)
  Ir_2_acq = rbinom(n=1, size=Is_2, p=pars$a_prop)
  Isa_2 = Isa_2 - Ira_2_acq
  Is_2 = Is_2 - Ir_2_acq
}
else {
  # As above, but no acquired resistance
  Is_2_tmp = sum(rpois(n=Isa_1, lambda=R_0_a))
  Is_2 = rbinom(n=1, size=Is_2_tmp, p=pars$sigma_vaxm*pars$sigma)
  Isa_2 = Is_2_tmp - Is_2
  Ira_2_acq = 0
  Ir_2_acq = 0
}

# Draw number DR secondary cases
Ir_2_tmp = sum(rpois(n=Ira_1, lambda=R_0_a))
# Determine number symptomatic
Ir_2 = rbinom(n=1, size=Ir_2_tmp, p=pars$sigma_vaxm*pars$sigma)
Ira_2 = Ir_2_tmp - Ir_2
# Supplement with acquired resistant cases
Ira_2 = Ira_2 + Ira_2_acq
Ir_2 = Ir_2 + Ir_2_acq

# If no cases in 2nd generation, skip to next iteration
# (No importation)
if (Ir_2 == 0 & Ira_2==0 & Is_2==0 & Isa_2==0 ) {
  num_zeros = num_zeros + 1
  next
}

# Initial conditions
init.values = c(
  S = N,
  Is = Is_2,    # DS, symptomatic, not on treatment
  Ts = 0,      # DS, symptomatic, on treatment
)
\[ \text{Ir} = \text{Ir}_2, \quad \text{# DR, symptomatic} \]
\[ \text{Isa} = 0, \quad \text{# DS, asymptomatic} \]
\[ \text{Ira} = 0, \quad \text{# DR, asymptomatic} \]
\[ \text{Rr} = 0, \quad \text{# DR, ever infected} \]
\[ \text{Rs} = 0, \quad \text{# DS, ever infected (excluding acquired resistance)} \]
\[ \text{Isa}_p = \text{Isa}_2, \quad \text{# asymptomatic peacekeepers DS} \]
\[ \text{Ira}_p = \text{Ira}_2 \quad \text{# asymptomatic peacekeepers DR} \]

\# Model transitions
\[
\text{transitions} = \text{list}(
\quad \text{c(S = -1, Is = +1)}, \quad \text{# infection (DS, becomes symptomatic)}
\quad \text{c(S = -1, Ir = +1)}, \quad \text{# infection (DR, becomes symptomatic)}
\quad \text{c(S = -1, Isa = +1)}, \quad \text{# infection (DS, becomes asymptomatic)}
\quad \text{c(S = -1, Ira = +1)}, \quad \text{# infection (DR, becomes asymptomatic)}
\quad \text{c(Is = -1, Ts = +1)}, \quad \text{# starting treatment (DS)}
\quad \text{c(Ts = -1, Ir = +1)}, \quad \text{# acquiring resistance on treatment}
\quad \text{c(Is = -1, Rs=+1)}, \quad \text{# death/recovery DS symptomatic}
\quad \text{c(Ir = -1, Rr=+1)}, \quad \text{# death/recovery DR symptomatic untreated}
\quad \text{c(Ts = -1, Rs=+1)}, \quad \text{# death/recovery DS symptomatic treated}
\quad \text{c(Isa = -1, Rs=+1)}, \quad \text{# death/recovery DS asymptomatic}
\quad \text{c(Ira = -1, Rs=+1)}, \quad \text{# death/recovery DR asymptomatic untreated}
\quad \text{c(Isa}_p = -1, Rs=+1)}, \quad \text{# death/recovery asymptomatic peacekeepers DS}
\quad \text{c(Ira}_p = -1, Rr=+1) \quad \text{# death/recovery asymptomatic peacekeepers DR}
\)

\# Rates transitions occur
\[
\text{RateF} \leftarrow \text{function(x, p, t) }
\quad \text{return(c}(
\quad \text{psigma}*(p\text{beta}^*x["S"]*x["Is"] + p\text{beta}_a^*x["S"]*x["Isa"] +}
\quad \text{p\text{beta}_t^*x["S"]*x["Ir"] + p\text{beta}_a^*p\text{beta}_vaxm^*x["S"]*x["Isa"], # DS infection symptomatic}
\quad \text{psigma}*(p\text{beta}^*x["S"]*x["Ir"] + p\text{beta}_a^*x["S"]*x["Ira"] +}
\quad \text{p\text{beta}_a^*p\text{beta}_vaxm^*x["S"]*x["Ira"], # DR infection symptomatic}
\quad (1-psigma)*(p\text{beta}^*x["S"]*x["Is"] + p\text{beta}_a^*x["S"]*x["Isa"] +}
\quad p\text{beta}_a^*p\text{beta}_vaxm^*x["S"]*x["Ira"], # DR infection asymptomatic)
\quad (1-psigma)*(p\text{beta}^*x["S"]*x["Ir"] + p\text{beta}_a^*x["S"]*x["Ira"] +}
\quad p\text{beta}_a^*p\text{beta}_vaxm^*x["S"]*x["Ira"], # DR infection asymptomatic)
\quad p\text{sigma}*["Is", # starting treatment (DS)
\quad p\text{sigma}*["Ir", # death/recovery DS symptomatic untreated}
\quad p\text{gamma}*["Ir", # death/recovery DR symptomatic untreated}
\quad p\text{gamma}_\text{ab}*["Ts", # death/recovery DS symptomatic treated}
\quad p\text{gamma}_a*["Isa", # death/recovery DS asymptomatic}
\quad p\text{gamma}_a*["Ira", # death/recovery DR asymptomatic}
\quad p\text{gamma}_a*["Isa_p", # death/recovery DS asymptomatic peacekeepers}
\quad p\text{gamma}_a*["Ira_p" # death/recovery DR asymptomatic peacekeepers}
\quad )
\}
\]
# running the model
# tf = final time = 1000
results = as.data.frame(ssa.adaptivetau(init.values, transitions, RateF, pars, tf=1000))

# subtract initial cases among peacekeepers
res_inf <- results$Rr[length(results$Rr)] - Ir_2 - Ira_2
sens_inf <- results$Rs[length(results$Rs)] - Is_2 - Isa_2

# if no cases in the general population, skip to next iteration
# (no importation)
if (res_inf==0 && sens_inf==0) {
  num_zeros = num_zeros + 1
  next
}

# otherwise, we have had an importation event
nonzero_ind = T
}

# END while loop

# return number DR infections, number DS infections, number prior non-importations
return(c(res_inf, sens_inf, num_zeros))
}

} # END FUNCTION cholera_res_model

############################################################
# Setting up to call the model function
############################################################

# Seed to reproduce parameter sets
set.seed(0)

# Setting fixed parameters
pars_vec = list(
gamma = 1/5, # recovery/death symptomatic untreated
gamma_abx = 1/(5.0-2.74), # recovery/death DS symptomatic treated
gamma_a = 1/5, # recovery/death asymptomatic untreated
(same as symptomatic treated)
beta_am = 0.1, # multiplier to beta for asymptomatic (.01 and .5 sensitivity analyses)
beta_tm = 1, # multiplier to beta for treated
N = 1e6, # population size - host country (1e4 sensitivity)
N_imp = 500, # battalion size
delta = 1/1.55, # incubation period
sigma_vaxm = 1-0.65, #multiplier probability of symptoms if vaccinated (1 if no vaccination, 1-.65 otherwise)
beta_vaxm = 0.37, # multiplier transmissibility asymptomatic infections given vaccination (1 if no vaccination, 0.37 log, 0.0194 linear)
v_abx = 0.34 # risk ratio of infection on prophylaxis (sensitivity analyses for 0.18 proph more effective, 0.66 less effective)
)
pars_vec = unlist(pars_vec)

# Number of parameter sets to draw
num_iter = 10000

# Setting up a matrix of parameter draws
# Rows: parameter set draws
# Columns: parameters
pars = as.data.frame(matrix(1, ncol=length(pars_vec), nrow=num_iter))
colnames(pars) <- names(pars_vec)
pars <- as.data.frame(t(t(pars) * pars_vec))

# setting up variable parameters
# applying Latin Hypercube Sampling
num_var = 6
lhsmat <- randomLHS(num_iter, num_var)
pars$a_prop <- 10^(-5 + (-2 - -5)*lhsmat[,1]) # proportion acquiring resistance
pars$R0 <- 1.25 + (5 - 1.25)*lhsmat[,2] # basic reproductive number
pars$tau_prop <- .05 + (.5-.05)*lhsmat[,3] # proportion symptomatic receiving treatment
pars$dr_prev <- 0 + (.5-0)*lhsmat[,4] # DR prevalence in departure country
pars$j <- 0.5/1000 + (8/1000-0.5/1000)*lhsmat[,5] # cholera incidence in departure country
pars$gamma <- qbeta(lhsmat[,6], 242, 706) # probability of symptoms

# For each parameter set, do 1 iteration with prophylaxis and 1 without
pars$proph <- T
pars2 <- pars
pars2$proph <- F
pars <- rbind(pars, pars2)

# updating dependent parameters
pars$tau <- pars$tau_prop/(1-pars$tau_prop)*pars$gamma # rate starting treatment
pars$a <- pars$a_prop/(1-pars$a_prop)*pars$gamma_abx # rate acquiring resistance
pars$beta <- pars$R0/pars$N/(pars$gamma/sigma)*pars$beta_am/pars$gamma_a # transmission parameter (from symptomatic, not on treatment)
pars$beta_a <- pars$beta_am*pars$beta # transmission parameter from asymptomatic
pars$beta_t <- pars$beta_tm*pars$beta # transmission parameter from (effectively) treated

# prevalence incubation-phase asymptomatic among departures - no (effective) prophylaxis
E_a = with(pars, {j*(1-sigma_vaxm*sigma)/sigma*(1/delta)/(365.25) })
# prevalence infectious asymptomatic among departures - no (effective) prophylaxis
I_a = with(pars, {j*(1-sigma_vaxm*sigma)/sigma*(1/gamma_a)/(365.25) })
# prevalence incubation asymptomatic among departures - on (effective) prophylaxis
E_a_abx = with(pars, {v_abx*j*(1-sigma_vaxm*sigma)/sigma*(1/delta)/(365.25) })
# prevalence infectious asymptomatic among departures - on (effective) prophylaxis
I_a_abx = with(pars, {v_abx*j*(1-sigma_vaxm*sigma)/sigma*(1/gamma_abx)/(365.25) })
# Probability of infection at departure by resistance pattern and prophylaxis use
# assume acquired resistant cases still experience decreased infection risk,
# but same duration as if resistant
pars$p_ds = (E_a+I_a)*(1-pars$dr_prev)
pars$p_dr = (E_a+I_a)*(pars$dr_prev)
pars$p_ds_abx = (E_a_abx+I_a_abx)*(1-pars$dr_prev)*(1-pars$a_prop)
pars$p_dr_abx = with(pars,((E_a+I_a)*dr_prev + v_abx*(E_a+I_a)*(1-dr_prev)*a_prop))
pars$par_id <- seq(1,dim(pars)[1],by=1)

# Run for 2,000 importation events per parameter set
reps = 2000

# Set up to run model function calls in parallel
max_clusters <- 32
cl <- makeCluster(max_clusters)
# send the functions we need to the workers
junk <- clusterEvalQ(cl, library(adaptivetau))

# creating a large data frame (may print as csv)
# stores all outputs from model for each iteration of each parameter set
num_pars = dim(pars)[1]
output_mat_full <- data.frame(matrix(data=NA,nrow=num_pars*reps,ncol=4))
names(output_mat_full) <- c('nonzero_DR_values','nonzero_DS_values','prior_zeros','par_id')

# To make results reproducible regardless of the number of clusters
# Gather seeds for each individual run
rn_total <- num_pars*reps
seed.temp <- gather(rn_total,seed=1)
Seed <- matrix(nrow= rn_total,ncol=6)
for(i in 1:rn_total){
  Seed[i,] <- seed.temp[[i]][2:7]
}

# for each parameter set
for (i in 1:num_pars) {
  par_list = as.list(pars[i,])
  print(i)
  # matrix of random seeds for this parameter set
  rn_mat <- Seed[seq((i-1)*reps+1, i*reps, by=1),]
  # Output is a matrix
  system.time(output_vec <- parApply(cl, X=rn_mat,MARGIN=1, FUN=cholera_res_model, pars=par_list))
  output_df <- as.data.frame(t(output_vec))
  output_df$par_id <- i
  output_mat_full[seq(reps*(i-1)+1,reps*i,1),] <- as.matrix(output_df)
}

stopCluster(cl)

# Uncomment if you want model output as a csv (files are large)
# write.csv(pars,'R_parameters_rand_log_full.csv')
# write.csv(output_mat_full,'R_output_rand_log_full.csv')
data <- output_mat_full

# Creating a summary data frame
chol_ana <- as.data.frame(matrix(nrow = num_pars / 2, ncol = 6))

names(chol_ana) <- c('par_id', 'excess_import_prob_proph',
                      'excess_ev_DR_proph_cond',
                      'excess_ev_DR_proph', 'excess_ev_DS_proph', 'excess_ev_rec_abx')

for (i in seq(1, num_pars / 2, 1)) {
  # Which parameters
  chol_ana$par_id[i] <- i

  # Outputs for this parameter set with & without prophylaxis
  proph <- data[seq(((i - 1) * reps + 1, reps * i, 1)],]
  no_proph <- data[reps * num_pars / 2 + seq(((i - 1) * reps + 1, reps * i, 1)],]

  # Excess importation probability given prophylaxis
  chol_ana$excess_import_prob_proph[i] <- reps / (reps + sum(proph$prior_zeros)) -
                                         (reps / (reps + sum(no_proph$prior_zeros)))

  # Excess expected number DR cases given prophylaxis conditional on importation
  chol_ana$excess_ev_DR_proph_cond[i] <- mean(proph$nonzero_DR_values) -
                                         mean(no_proph$nonzero_DR_values)

  # Excess expected number DR/DS cases (unconditional)
  chol_ana$excess_ev_DR_proph[i] <- sum(proph$nonzero_DR_values)/
                                   (reps + sum(proph$prior_zeros)) -
                                   sum(no_proph$nonzero_DR_values)/
                                   (reps + sum(no_proph$prior_zeros))

  chol_ana$excess_ev_DS_proph[i] <- sum(proph$nonzero_DS_values)/
                                   (reps + sum(proph$prior_zeros)) -
                                   sum(no_proph$nonzero_DS_values)/
                                   (reps + sum(no_proph$prior_zeros))

  # Excess number of antibiotics provided (approximate)
  chol_ana$excess_ev_rec_abx[i] <- 500 +
                                 pars$tau_prop[i] * pars$sigma[i] * (sum(proph$nonzero_DR_values)/
                                 (reps + sum(proph$prior_zeros)) +
                                 sum(proph$nonzero_DS_values)/
                                 (reps + sum(no_proph$prior_zeros)) -
                                 sum(no_proph$nonzero_DS_values)/
                                 (reps + sum(no_proph$prior_zeros)))

  # Raw importation probabilities
  # chol_ana$import_prob_proph[i] <- reps / (reps + sum(proph$prior_zeros))
  # chol_ana$import_prob_noproph[i] <- reps / (reps + sum(no_proph$prior_zeros))
}

} # END for loop
# unconditional EV DR cases - crosses 0
chol_ana$proph_preferred <- NA
chol_ana$proph_preferred[which(chol_ana$excess_ev_DR_proph>0)] <- 0
chol_ana$proph_preferred[which(chol_ana$excess_ev_DR_proph>=0)] <- 1
chol_ana$proph_preferred[which(chol_ana$excess_ev_DR_proph>=0)] <- as.factor(chol_ana$proph_preferred)
a <- ggplot(data=chol_ana) + geom_histogram(aes(x=excess_ev_DR_proph, fill=proph_preferred)) +
  labs('Excess DR Infections (Overall)') + theme_bw() +
  geom_vline(xintercept = 0, linetype=2, col='grey', size=0.5) +
  labs('Count')
+scale_x_continuous(limits=c(0,1000), labels=comma)
+scale_fill_manual(values=c('lightblue','firebrick')) +
  guides(fill=FALSE) +
  ggtitle("A")

# importation probability max is negative
b <- ggplot(data=chol_ana) + geom_histogram(aes(x=excess_import_prob_proph), fill = "lightblue") +
  labs('Excess Importation Probability') + theme_bw() +
  geom_vline(xintercept = 0, linetype=2, col='grey', size=0.5)

# conditional EV DR cases (min is positive)
c <- ggplot(data=chol_ana) + geom_histogram(aes(x=excess_ev_DS_proph_cond), fill='firebrick') +
  scale_x_continuous(labels=comma) + labs('Excess DR Infections (Given Importation)') +
  theme_bw() +
  labs("Count") +
  geom_vline(xintercept = 0, linetype=2, col='grey', size=0.5)

# for parameters where prophylaxis leads to excess DR cases
# average DS cases prevented per excess DR case
# note log scale.
chol_ana$ratio_DS_DR <- NA
chol_ana$ratio_DS_DR[which(chol_ana$excess_ev_DS_proph>0)] <-
  chol_ana$excess_ev_DS_proph[which(chol_ana$excess_ev_DS_proph>0)]/
  chol_ana$excess_ev_DR_proph[which(chol_ana$excess_ev_DR_proph>0)]
d <- ggplot(data=chol_ana) + geom_histogram(aes(x=ratio_DS_DR), fill = "lightblue") +
  scale_x_log10(breaks=c(1,10,100,1000,10000), labels=comma) +
  labs('DS Infections Prevented per Excess DR Infection') +
  theme_bw() +
  labs("Count")

# how many get antibiotics? (averages)
chol_ana$proph_preferred_abx <- NA
chol_ana$proph_preferred_abx[which(chol_ana$excess_ev_rec_abx<0)] <- 0
chol_ana$proph_preferred_abx[which(chol_ana$excess_ev_rec_abx>=0)] <- 1
chol_ana$proph_preferred_abx[which(chol_ana$excess_ev_rec_abx>=0)] <- as.factor(chol_ana$proph_preferred_abx)
e <- ggplot(data=chol_ana) + geom_histogram(aes(x=excess_ev_rec_abx, fill=proph_preferred_abx)) +
  labs('Excess Individuals Receiving Antibiotics ') +
  theme_bw() +
  geom_vline(xintercept = 0, linetype=2, col='grey', size=0.5) +
  labs("Count") +
  scale_fill_manual(values=c('lightblue','firebrick')) +
  guides(fill=FALSE) +
  scale_x_continuous() +
  guides(fill=FALSE)

chol_ana_pars <- merge(chol_ana,pars,by="par_id")

# PRCCs with CI's
X1 <- with(chol_ana_pars,{cbind(j,dr_prev,R0,a_prop,sigma,tau_prop)})
out1 <- pcc(data.frame(X1), chol_ana_pars$excess_ev_DR_proph, rank=T, nboot=1000)
out1
X2 <- with(chol_ana_pars, {cbind(j, dr_prev, R0, a_prop, sigma, tau_prop)})
out2 <- pcc(data.frame(X2), chol_ana_pars$excess_ev_DS_proph, rank=T, nboot=1000)
out2
X3 <- with(chol_ana_pars, {cbind(j, dr_prev, R0, a_prop, sigma, tau_prop)})
out3 <- pcc(data.frame(X3), chol_ana_pars$ratio_DS_DR, rank=T, nboot=1000)
out3

######################################################################
############################## END CODE ###############################
######################################################################