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MODELING TARGETED IVERMECTIN TREATMENT FOR CONTROLLING RIVER BLINDNESS

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Abstract

There is considerable host heterogeneity in exposure to onchocerciasis. We incorporate this heterogeneity into a model of onchocerciasis transmission that we use to evaluate intervention strategies targeting specific portions of the human population for treatment with ivermectin. Our model predicts that targeted allocation of ivermectin in a highly heterogeneous population will reduce the public health burden of onchocerciasis using 20–25% of the doses of untargeted allocation. Targeted allocation therefore poses significantly lower risk of adverse effects, while potentially delaying the emergence and spread of ivermectin resistance, relative to untargeted allocation.

INTRODUCTION

The filarial parasite *Onchocerca volvulus* causes onchocerciasis (river blindness) in humans. In addition to keratitis leading to the eponymous river blindness, clinical manifestations include debilitating pruritus, fatigue, malnutrition, stigmatizing skin lesions such as depigmented “leopard skin,” and the frequently superinfected, hyperreactive sowda form. The morbidity associated with onchocerciasis totals an estimated 950,000 disability-adjusted life years (DALYs) each year, primarily in Africa.^{1,2} The economic burden to less developed countries of leaving land fallow due to the threat of onchocerciasis amounts to hundreds of millions of dollars annually.³

The life cycle of *O. volvulus* involves humans as the definitive host. Adult worms typically survive for over a decade in onchocercomata—subcutaneous nodules in the human host (Figure 1). The female worm produces millions of microfilariae, the first larval stage. The microfilariae are ingested by the *Simulium* black fly vector during a blood meal, wherein they mature to third stage larvae (L3). The propensity of *Simulium* to breed in fast-flowing water lends onchocerciasis its common name. The larvae reenter humans during later blood meals, where they mature into adult parasites.

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Ivermectin is an antimicrofilarial agent that acts as secondary prevention in infected individuals, reducing microfilarial survival and hence the burden of disease.⁴ Ivermectin also provides primary prevention for the community by decreasing the number of microfilariae picked up by *Simulium* during blood feedings, thus reducing transmission.^{5,6} Since the establishment of the Mectizan™ Donation Program (MDP) by Merck and Co., Inc., more than 525 million tablets of ivermectin have been distributed, mostly through programs that use community-directed treatment with ivermectin (CDTI), an untargeted allocation strategy.⁷ Ivermectin has no significant macrofilaricidal activity and only moderate long-term effects on macrofilarial fertility, necessitating repeated treatment.^{8,9} Ivermectin alone is unlikely to achieve onchocerciasis eradication in many parts of Africa, due to operational difficulties and epidemiologic conditions in hyperendemic communities.^{10–14}

Other means of combating onchocerciasis are limited. Vector control has been the mainstay of efforts in West Africa through the Onchocerciasis Control Program (OCP), but the OCP ended in 2001 and the risk of recrudescence remains.¹⁰ The existing macrofilaricidal medication used against *O. volvulus*, suramin, carries significant risk of adverse effects that makes it unsuitable for wide-scale use.⁹ No effective vaccine exists and considerable barriers to its development remain.¹⁵ The hope of stimulating a protective immune response using a vaccine is tempered by the inability to develop highly protective immunity in the natural course of infection,¹⁶ and the possible circulation of multiple antigenic strains.¹⁷

Untargeted allocation of ivermectin carries public health risks and economic costs. Individuals coinfecting with *Loa loa* are at risk of encephalopathy when ivermectin treatment leads to the death of large numbers of *Loa* microfilariae in the brain.¹⁸ Concern for such adverse effects in field sites in southern Sudan motivated our quantitative evaluation of targeted ivermectin allocation. Additionally, moderate protective immunity to *O. volvulus* may be lost during treatment, increasing the risk of heightened morbidity should ivermectin treatment end; this has been observed in the related *Onchocerca chengi* in cattle.¹⁹ Finally, recent studies in Ghana point to the emergence of *O. volvulus* resistant to ivermectin. Wide-scale treatment may hasten the emergence and spread of such resistance.²⁰

For many macroparasites, overdispersion of parasites among hosts means fewer than 20% of hosts are responsible for more than 80% of transmission, the “20/80 rule”.^{21,22} If the high-transmission subpopulation may be inexpensively targeted, a disproportionate public health benefit may be acquired with decreased cost—both medical and economic.²³ Successful targeted chemotherapy programs have been used in the control of other helminths, such as *Ascaris lumbricoides* and *Schistosoma haematobium*.^{24–26} Profiles of onchocercal microfilarial burden within human populations reveal aggregation of parasite burden, conforming to a common negative binomial distribution.^{27,28} This aggregation has been attributed to differences in host exposure to the black fly vector,^{12,29,30} but immunologic or other factors may also play a role.^{28,31,32} Irrespective of the underlying determinants, the aggregation of onchocerciasis infection may make targeted allocation an effective intervention strategy.

Identifying the high-transmission subpopulation is fundamental to any targeted allocation strategy. For public health planning, much research has already been conducted to identify communities at elevated risk,^{33,34} but identification of heavily infected individuals is more difficult.¹² The gold standard for diagnosis, microscopic examination of skin snips, is resource intensive and limited in sensitivity; part of the attraction of mass treatment is avoidance of this technique.⁹ The potential of other symptoms and signs as indicators of heavy infection, for example the presence of onchocercomata or failing a simple visual acuity test,³⁵ require further investigation. The development of field dipstick tests based on

onchocercal antigens³⁶ may also provide a relatively simple means of identifying the heavily infected. Research into the key determinants of the aggregated distribution will also be important.^{28–32} Thus, while no simple means of targeting therapy has been field-tested, there are multiple lines of inquiry that may lead to fruitful methods.

Mathematical models have been developed to address decision-making about community ivermectin treatment duration, larvicidal vector-control strategies, and recrudescence probabilities; as well as to help tease out important life cycle parameters.^{11,33–35} These models have incorporated heterogeneity of vector contact rates for different humans within a community. Here we develop and analyze a model of onchocerciasis control with ivermectin that incorporates selective targeting of highly exposed subpopulations—an intervention neglected by previous models, which may become increasingly attractive as understanding of transmission heterogeneity improves.

MATERIALS AND METHODS

A model of *O. volvulus* transmission within human sub-populations was designed to examine interactions among heterogeneity in host exposure, parasite aggregation, and effectiveness of targeted versus untargeted ivermectin allocation strategies (Figure 2). Model parameters are described later in this paragraph and summarized in Table 1.

Our model incorporated the human heterogeneity underlying the aggregated parasite distribution by defining human subpopulations according to their contact shares with the *Simulium* vector. Contact shares are defined as the proportion of all human-fly contacts that include members of that subpopulation. Rates of contact appear to be important in explaining distributions of onchocercal burden.³⁰ For each subpopulation, contact shares were assumed to be identical whether transmitting microfilariae or becoming infected by L3 larvae. This approach facilitated modeling the treatment of human subpopulations with different ivermectin coverage levels. This approach also improves upon population-wide modeling of average macrofilarial burden or community microfilarial load as a proxy for disease burden since the risk of some sequelae, including blindness, rises non-linearly and displays threshold effects with worm load.³³

Female macrofilarial populations were compartmentalized according to the subpopulation of human hosts in which they were harbored; our model is thus of the “parasite in human host” form discussed by Basáñez and colleagues.³⁵ Macrofilariae were further divided by number of past treatments with ivermectin, as repeated treatment has been observed to progressively reduce female fecundity.⁸ This compartmentalization generated the worm subpopulations w_{vi} where v is the number of prior treatments sustained by the worm subpopulation and i the index of the human subpopulation in which they are harbored. Worms treated a fifth time were removed from the population; their reproductive contribution was negligible. Mortality for both human and worm populations was assumed to occur at constant rates μ_h and μ_w ;³⁶ total natural mortality for worms is thus the chance that either the worm or its host dies: $\mu_n = 1 - (1 - \mu_h)(1 - \mu_w)$. We used a value of 1/33 for μ_h , and 1/12 for μ_w .^{1,30} The mortality rate for the worm population may be equivalently interpreted as the inverse of the macrofilarial reproductive lifespan.

The i human subpopulations were defined by their contact shares, c_i , and population shares, n_i , each of which sum to unity across the human population. Human population size was constant with births balancing deaths. Functionally, human births contribute no worms to the population. Each sub-population can be treated with a separate ivermectin cover-age rate t_i . Cumulative larval survival rates at each stage of development are subsumed into the reproductive rate.

A basic reproductive rate, R_0 , of macroparasites is defined as the lifetime number of adult female worms produced by each adult female worm in the absence of density-dependent constraints.²⁷ The R_0 of *O. volvulus* in a specific community is the product of diverse epidemiologic, entomologic, and environmental factors and reflects the behavior of the system in the absence of ivermectin treatment. The R_0 implicitly assumes host homogeneity, so we must superimpose host heterogeneity. Thus, we use an R_0 quantified to remain constant in the model as we varied population heterogeneity and ivermectin treatment, allowing us to isolate the impact of these parameters. The R_0 for particular communities with endemic *O. volvulus* has been estimated to range from 3.1–66.7;³³ recent estimates have been significantly lower, down to 5 to 8.³⁰ We modeled values of R_0 from 1–50.

Our model is applicable for vector species such as *S. damnosum s.l.* in Africa or *S. metallicum s.l.* in Venezuela that lack well-developed cibarian armature, as we do not include initial facilitation in density-dependent uptake of microfilariae.^{37,38} However, as our model directly incorporates R_0 as the product of multiple entomologic and epidemiologic factors, it implicitly allows for differences in vector competency as between those species.

All adult females are assumed to be fertilized. This approximation generates an elevated estimation of the utility of indiscriminate treatment of low-burden hosts. This is therefore a conservative assumption in comparing the effectiveness of targeted treatment relative to untargeted treatment.³⁹ We incorporate density dependence of parasite fecundity, as observed in many helminths.²⁷ Since R_0 is a lifetime measure, we can define the annualized basic reproductive number per parasite, f_0 , as R_0/μ_n . The total number of worms entering the human population, N , annually is

$$w_{new} = N f_0 \sum_i P_i g_i c_i \sum_v \sigma^v \bar{w}_{vi}.$$

The variable g_i is the adjustment for parasite density in human subpopulation i . The variable P_i adjusts for current treatment of subpopulation i , while σ^v adjusts for treatment in previous years. The variable c_i adjusts for the weighting of contacts of subpopulation i . The average number of adult female parasites by human subpopulation and treatment history is denoted $\bar{w}_{vi}$. Parasite fecundity of the adult females is assumed to decline permanently with each ivermectin treatment to a fraction, σ , of prior fecundity; after 4 treatments worms make negligible contributions to parasite reproduction. Empirical studies suggest $\sigma = 70\%$.⁸

Treatment is assumed to cause instantaneous elimination of all living microfilariae, followed by replenishment of skin microfilariae at a rate that will achieve the new fraction of fertility, σ , after a duration of 1.5 years—the approximate microfilarial lifespan l_{mf} ,³⁶ representing the time to equilibrium.³⁶ The area under the curve of recovering microfilarial load over time is then $\rho = (\sigma \Delta t) / (2 l_{mf})$, where Δt is the time increment of 1 year. The time step of 1 year was chosen to capture annual treatments with ivermectin.^{1,36} We confirmed that smaller time steps give the same quantitative predictions. The microfilariae-mediated reduction in reproduction, given that a fraction t_i of the population is treated, is thus $P_i = 1 - t_i(1 - \rho)$.

The density dependence of fertility is based on a Beverton Holt function, where $g_i = (1 + \gamma) / (1 + \gamma \bar{w}_i)$, $\gamma = 0.3$ is a measure of the magnitude of the dependence, $\bar{w}_i$ is the average per person worm burden in subpopulation i , and $g_i(1) = 1$. This is similar to the density dependence modeled in other helminths,⁴⁰ and is conservative here in that it discounts contribution to transmission from the most heavily infected individuals. While 3 has been estimated at 0.034 when relating microfilarial density to human worm burden,⁴¹ our model

implicitly incorporates additional sources of density dependence such as declining microfilarial fitness with burden and crowding within the vector.

Newly maturing worms infect the human subpopulations in proportion to their contact shares. When the equations are discretized, the worm population within any compartment at time $t + 1$, $w_{vi}(t + 1)$ becomes:

$$w_{vi}(t+1) = \begin{cases} (1 - \mu_n)(1 - t_i)w_{vi}(t) + c_i w_{new}(t) & \text{for } v=0 \\ (1 - \mu_n)(1 - t_i)w_{vi}(t) + (1 - \mu_n)t_i w_{(v-1)i}(t) & \text{for } 1 \leq v \leq 4 \\ 0 & \text{for } v > 4 \end{cases}$$

Numerical simulations were carried through to infection equilibrium from populations initiated with at least 1000 worms. Baselines were simulated with three different distributions of exposure: uniform, moderately heterogenous, and highly heterogenous (Table 2). The moderately heterogenous and highly heterogenous distributions have been used previously; the highly heterogenous distributions has been found by Woolhouse and colleagues to describe a broad range of parasitic infections.^{21,33} Field studies have revealed such heterogeneities in human populations subject to onchocerciasis.^{12,28,30} For each of the distributions, 4 different treatment regimens were then simulated and compared with the corresponding baseline: effective treatment with ivermectin coverage of 30%, 60%, or 90% of the target population, with the target population representing either the entire human population or the subpopulation with the highest contact share. The lower 2 coverage rates are typical for other public health programs; the highest rate has been achieved in some locations with programs of community-directed treatment with ivermectin (CDTI).^{42,43}

RESULTS

The model settled into stable equilibria in all numerical simulations. An approximately linear relationship between R_0 and mean population worm burden at higher R_0 arises from density-dependent reproduction (Figure 3). Ivermectin treatment of the uniform population results in coverage-dependent percentage decreases in mean worm burden relatively constant across R_0 and between levels of coverage. Treatment above a critical percentage for low values of R_0 achieves onchocerciasis eradication.

Examination of worm burden within different population structures shows a predictable differential of mean burden between high and low contact subpopulations (Figure 4). For the non-uniform population structures, the whole-population mean worm burden is the same as that of the uniform population once $R_0 > 2$ (results not shown). This reflects the rapid plateau reached in worm reproduction with the Beverton Holt function and the value of 0.3 for γ : high worm burdens make diminishing contributions to reproduction. At low R_0 , untargeted treatment of heterogeneous populations results in smaller reductions in worm burden than when uniform populations are treated. At higher R_0 , however, the populations experience similar reductions with untargeted treatment. Furthermore, targeted treatment reduces worm burden more than untargeted treatment.

When the percent reduction in mean worm burden is divided by the fraction of the whole population covered, producing a per-dose estimate of the effectiveness of treatment programs, targeted treatment of a highly heterogeneous population reveals itself to be 1.8 to 3.2 times as effective (Figure 5). Moderately heterogeneous population structures produce less pronounced differences in effectiveness. This result is robust across the full range of R_0 values tested.

Since the burden of onchocerciasis is subject to threshold effects, the population disposed to the highest worm burden bears a disproportionate share of the health burden. Dietz has estimated that the prevalence of severe sequelae such as eye lesions and blindness are exponential functions of worm burden.³³ Thus we compared percent reductions rather than absolute reductions in worm burdens. When examining specifically the high contact subpopulation, similar predictions arise as for the overall population: targeted doses are more effective in reducing worm burdens.

In light of the desire to limit worm burden among the most exposed, we modified the model to solve for the necessary level of targeted ivermectin coverage to reduce mean worm burden in the high contact subpopulation below a target level. For any R_0 , if such a reduction is possible solely using targeted treatment it occurs at a lower ivermectin coverage level than with untargeted treatment (Figure 6). In the highly heterogeneous structure at field values of R_0 (e.g., < 25) the targeted reduction is possible with 20–25% of the doses necessary for the untargeted reduction. This result is robust for target worm burdens ranging from 1–100, for shorter time steps down to 3 months, and for human and worm mortality rates up to 1/40 and 1/15. At significantly higher R_0 the reduction goal requires treatment of the low contact subpopulation as well. At this point the necessary population treatment level rises steeply since the low contact subpopulation represents less efficient ivermectin use. If our model discounted less steeply the contribution to reproduction of high burden individuals, the inflection point would be shifted to a higher R_0 .

DISCUSSION

We quantitatively assessed the relative effectiveness of targeted versus untargeted ivermectin allocation in populations of different levels of host exposure heterogeneity and *O. volvulus* R_0 . At levels of R_0 found in field locations,^{30,33} and at levels of human contact rate heterogeneity found in other macroparasites and suggested in *O. volvulus*,^{21,30,33} targeted treatment with ivermectin can reduce equilibrium microfilarial burdens below arbitrary target burdens with only 20–25% of the doses required for untargeted treatment (Fig. 6). Our model provides a conservative evaluation of the effectiveness of targeted treatment in many respects. The Beverton Holt function used for density dependence of the recruitment function for new adults is compensatory, so that contribution to worm reproduction of highly infected individuals plateaus at a level of approximately 3 adult females per host. This density dependence sharply reduces the effect of heterogeneity in host-vector contact rates. Our estimate of human mortality rate, supported by field data from a number of endemic sites,³⁰ is conservative in that longer human life spans would increase the effectiveness of treatment. Additionally, reductions in microfilarial burden are examined from an equilibrium perspective. As treatment with ivermectin temporarily reduces microfilarial burden over the following year, and as such burdens are higher in more heavily infected individuals, the transient reduction in microfilarial burden from ivermectin will be greatest in the high contact subpopulation, thus further increasing the relative effectiveness of targeted allocation in terms of microfilariae prevented. Moreover, there are important threshold effects in onchocerciasis-related morbidity, with the prevalence of blindness disappearing in villages under certain levels of transmission.³³ For all sequelae of onchocerciasis that exhibit exponential relationships between risk and worm burden, effectiveness of targeted allocation is even greater on a percent-for-percent basis than that of untargeted allocation: the reductions in targeted therapy bring individuals down steeper portions of the risk curves than those of untargeted therapy. Thus, the effectiveness of targeted therapy in reducing morbidity per dose is likely to be even more pronounced than is reflected in this model.

If untargeted allocation were able to eradicate onchocerciasis through eliminating transmission, the relative effectiveness argument might be moot. However, consensus is growing that sufficient suppression of transmission is untenable in many African foci.^{10,11,13,14,44} Meanwhile, the threat of encephalopathy associated with ivermectin treatment in those infected by *L. loa* poses a public health cost to treatment. Moreover, treatment may carry long-term costs. First, the emergence and spread of ivermectin-resistant *O. volvulus* may be hastened according to the number of doses distributed, and has already been suspected in an area of Ghana subject to long-term treatment.²⁰ Second, cessation of treatment may leave individuals with diminished immunity, susceptible to levels of infection associated with even higher morbidity, as seen in the cattle/*O. ochengi* model.¹⁹ Further research into the development and loss of protective immunity will be important to assess this potential outcome. Ivermectin treatment also carries economic costs in terms of labor, supplies, and capital for the maintenance of public health infrastructure. Finally, additional methods for managing onchocerciasis are not readily available; the structural similarity of moxidectin to ivermectin suggests it will suffer from cross-resistance,² and the development of an effective vaccine still faces numerous obstacles.¹⁵ Given the costs surrounding ivermectin use, and the shortage of substitutes should it eventually fail, ivermectin should be viewed as a limited resource whose public health utility must be maximized.

Community-directed treatment with ivermectin (CDTI) carries additional benefits beyond those related simply to onchocerciasis. CDTI may incidentally treat scabies, *Ascaris*, and the lymphatic filariases. Other public health programs may piggyback on the infrastructure erected for CDTI—but they may equally benefit from the infrastructure for targeted programs.^{45,46} Thus, while concerns unrelated to onchocerciasis enhance the attractiveness of community-directed untargeted treatment, targeted programs may carry similar organizational benefits.

Targeted therapy within our model focuses on those individuals with the highest contact rates with the vector. In practice, targeting could take place based on symptoms. Such symptom-targeted allocation may have a similar relative effectiveness in reducing worm burden compared with contact-targeted allocation. In either case, the ease of identifying the target population will be critical, as the cost of CDTI per dose delivered may be less than targeted therapy unless screening methods are inexpensive.²³ Emukah and colleagues conducted a simple visual screening that could function as an indicator; the observed decrease in prevalence of visual impairment (94%) over the 8 years of treatment suggests the deficits were due to onchocerciasis.⁴⁷ Screening for onchocercomata can be easily integrated into CDTI programs, and provides a specific test of worm burden.⁴⁸ Individual indicators might be extended from community indicators that have been developed to easily identify village-level risk.⁴⁸

Targeted chemotherapy has a history of reducing the disease burden associated with various helminth infections.^{24–26} Aggregation of worm burden is well known in onchocerciasis,²⁸ and has been regarded as fundamental in design of control programs.³⁵ Here we show that targeted treatment could effectively make use of host heterogeneity and resultant infection aggregation. The potential public health benefit of targeted therapy calls for further research into heterogeneity of worm burden. In particular, methods for the identification of highly exposed individuals and neighborhoods require investigation.

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Figure 1. Life cycle of *Onchocerca volvulus*. Transmission between vector and human host occurs during blood meals.

Figure 2.

Structure of onchocerciasis model. See text and Table 1 for parameters. New worms enter the model and infect human subpopulations according to contact rates. Each row is a separate human subpopulation. Arrows across a row represent treatment of worms with ivermectin, progressively decreasing worm fecundity. Dotted lines represent ellipsis in the relevant direction.

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Figure 3.

Mean worm burden in a uniform population according to R_0 and ivermectin coverage. Both axes are logarithmic. Mean worm burdens below 1 indicate ivermectin treatment at the corresponding level would eradicate *O. volvulus* given sufficient time.

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Figure 4.

Separation of worm burdens in low and high contact subpopulations. MH = moderately heterogeneous population, HH = highly heterogeneous population. See Table 2 for contact shares.

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Figure 5.

Relative effectiveness per dose of targeted vs. untargeted strategies. The y-axis represents percent reduction in mean worm burden divided by number of doses given, normalized against the values for each corresponding untargeted strategy. All untargeted strategies, therefore, lie horizontally at 1. Percents in the legend represent fraction of the entire population treated.

Figure 6. Percent of population that must be treated to limit mean worm burden in the high contact subpopulation of a highly heterogeneous population to below 40. Note that x-axis is linear.

Table 1

Model variables and parameters

Parameter	Description	Values
c_i	Share of vector-human contacts occurring with subpopulation i ^{21,33}	See Table 2
n_i	Share of humans in subpopulation i ^{21,33}	See Table 2
N	Human population	1000
σ	Fraction adult fecundity remaining per treatment ⁸	70%
ρ	Fraction of microfilariae production adjusting for ivermectin treatment of single worm	$\frac{\sigma \Delta t}{2l_{mf}}$
P_i	Fraction of microfilariae output adjusting for treatment across subpopulation i	$1 - t_i(1 - \rho)$
t_i	Fraction of humans treated with ivermectin in subpopulation i ^{42,43}	0%, 30%, 60%, 90%
R_0	Basic reproductive number for <i>Onchocerciasis</i> in community ^{30,33}	1–50
f_0	Annual contribution to R_0	$R_0(\mu_w + \mu_h)$
μ_w	Worm mortality rate ¹	1/12
μ_h	Human mortality rate ³⁰	1/33
g_i	Fraction of full microfilariae output adjusting for density dependence, subpopulation i	$\frac{1+\gamma}{1+\gamma \bar{w}_i}$
γ	Parameter for density dependence of microfilariae production (c.f. ⁴¹)	0.3
l_{mf}	Microfilarial lifespan ³⁶	1.5 years
Δt	Model time increment	1 year
w_{vi}	Number of worms treated v times in subpopulation i	Simulated
w_{new}	New worms introduced in a year	$N f_0 \sum_i P_i g_i c_i \sum_v \sigma^v \bar{w}_{vi}$
$\bar{w}_i$	Average worm burden within subpopulation i	$\sum_v \frac{w_{vi}}{N n_i}$
$\bar{w}_{vi}$	Average burden of worms treated v times with ivermectin within subpopulation i	$\frac{w_{vi}}{N n_i}$

See text for explanations and parameter sources.^{1,33,36,41}

Table 2

Human population structures

Structure	Population shares	Contact shares
Uniform (U)	$n_1 = 1$	$c_1 = 1$
Moderately heterogeneous ³³ (MH)	$n_1 = 0.5$	$c_1 = 0.8$
	$n_2 = 0.5$	$c_2 = 0.2$
Highly heterogeneous ²¹ (HH)	$n_1 = 0.2$	$c_1 = 0.8$
	$n_2 = 0.8$	$c_2 = 0.2$