The control of infectious diseases
from the perspective of mathematical models
Die Bekämpfung von Infektionskrankheiten
aus der Sicht mathematischer Modelle

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Für Simon
Preface

The World Health Organization (WHO) states in its agenda: "One of the greatest threats to international health security arises from outbreaks of emerging and epidemic-prone diseases", suggesting that their control is a paramount goal of the international community.

The successful control of infectious diseases requires a systematic and strategic course of action which may demand decades of control to reach a pre-defined target. In such a process, mathematical models and computer simulations help us to optimize intervention strategies prospectively.

Infectious diseases

Epidemic-prone and emerging diseases are predominantly infectious diseases which either are transmitted directly (from human to human) or indirectly (e.g. by insects).

Infectious diseases spread by transmission and thus, measures of intervention or prevention aim at a reduction of transmission or contagiousness. Control measures are time-dependent, dynamic processes with a feedback on the process itself: reducing transmission decreases the incidence of further infections which further reduces transmission. The course of such feedback processes can be predicted.

Due to this potential predictability of the transmission processes, the planning of control programmes needs not solely to rely on experiments, studies or empiric knowledge collected otherwise. These programmes can be efficiently supported by mathematical and computational methods which predict the expectation or the probability of intervention success.

Models - past and future

The paper of Ronald Ross, who investigated in 1911 the transmission of malaria, can be regarded as first application of a dynamic model in the field of infectious disease epidemiology. Kermack und McKendrick have developed this methodology further in a series of five papers published in the 1920s.

Mathematical approaches have received strong support by the computational techniques of the recent decades. Thus, contemporary approaches can consider, for example, spatial transmission, contact networks in the population, household structure, immunity, specific interventions, and demography. Models become increasingly complex and require then to be computed on clusters.

Deterministic and stochastic models

Mathematical models in the field of infectious diseases epidemiology can be classified into deterministic and stochastic approaches. Deterministic models are usually based on differential or difference equations, depending on whether a continuous or discrete time-scale is of interest. Both
approaches have in common that there solution always describes an expected value only.

Stochastic approaches on the other hand can additionally consider the variability around the expected value and can quantify the occurrence of events in terms of probabilities. If random variation is not considered, these models reproduce always the same outcome when started from identical initial conditions.

If it is necessary to consider influences of random variation, deterministic and stochastic approaches can be implemented on a computer together with a random number generator. This is a more realistic approach, because natural processes are subject to random fluctuation even when initialized with identical conditions.

**When which model?**

Not every model can be used to answer a specific question; in other words: "... It is of course desirable to work with manageable models which maximize generality, realism and precision toward the overlapping but not identical goals of understanding, predicting, and modifying nature. But this cannot be done...". As a rule of thumb, we could state that deterministic models yield results which can more easily be generalized while being less realistic. Stochastic models, on the other hand, are more realistic, but their results are more difficult to interpret and to generalize.

Despite this methodological dilemma, there is a central quantity in infectious disease epidemiology by which the self-multiplying nature of the infection process can be expressed - the basic reproduction number $R_0^{35,36,40,41}$. It describes the number of secondary infections originating from one index case in a fully susceptible population. At first, this definition holds only when interventions are not performed, but it can be extended to include them$^{42,43}$.

**Motivation**

The present manuscript shows how deterministic and stochastic models support the planning of control measures against infectious diseases. They can be used to evaluate and predict the prospects of success of these measures.

Our intention to shift a natural and evolutionary "proven" equilibrium towards a state in which our well-being profits from this shift harbours the risk of erroneous and counterproductive concepts. Models as tools of systems biology help us to understand a system as a whole, to think more prospectively, and to evaluate the consequences of intended strategies.

Part A shows this in the example of influenza, representing a directly transmitted disease. Predictions computed by the deterministic model InfluSim show that an influenza pandemic can be controlled much more efficiently if an intervention based on antiviral drugs will be complemented by measures of contact reduction, even if contact rates in the population are reduced only slightly (chapter 1). The stochastic model indicates that the course of the pandemic as well as the success of the intervention is strongly determined by the contact network in the population (chapter 2). This contact network is, however, largely unknown and thus,
our expectations of the prospects of success of these interventions underlie substantial uncertainties.

In part B, an indirectly transmitted disease is represented by the example of onchocerciasis, a vector-borne disease which is transmitted by flies and mainly prevalent in Africa. The deterministic model shows that the eradicability of onchocerciasis strongly depends on the degree of the non-linear relationship between the force of infection and the actual infection rate of human hosts (chapter 3). The quantitative relationship between these two rates is estimated by means of a stochastic approach (chapter 4). Also other non-linear dependencies in the parasite-host-relationship promote the persistence of the parasite in the human population and determine the eradicability of the infection. The examples show that insufficient knowledge about the interaction between the parasite and the host challenges our expectations with respect to the success of interventions.

Mathematical models and simulations enable insights into processes which cannot be investigated by other methods. This refers in particular to control programmes whose target lines are located in the future so that considerations into the prospects of intervention success necessarily must rely on model predictions. In these situations, models help us to discriminate between likely and unlikely expectations, and between useful and useless interventions.
Influenza pandemic preparedness plans are currently developed and refined on national and international levels. Much attention has been given to the administration of antiviral drugs, but contact reduction can also be an effective part of mitigation strategies and has the advantage to be not limited per se. The effectiveness of these interventions depends on various factors which must be explored by sensitivity analyses, based on mathematical models.

We use the freely available planning tool InfluSim to investigate how pharmaceutical and non-pharmaceutical interventions can mitigate an influenza pandemic. In particular, we examine how intervention schedules, restricted stockpiles and contact reduction (social distancing measures and isolation of cases) determine the course of a pandemic wave and the success of interventions.

A timely application of antiviral drugs combined with a quick implementation of contact reduction measures is required to substantially protract the peak of the epidemic and reduce its height. Delays in the initiation of antiviral treatment (e.g. because of parsimonious use of a limited stockpile) result in much more pessimistic outcomes and can even lead to the paradoxical effect that the stockpile is depleted earlier compared to early distribution of antiviral drugs.

1.1. Introduction

The recent spread of highly pathogenic avian influenza from Asia to Europe and the transmission to humans has intensified concerns over the emergence of a novel strain of influenza with pandemic potential. While still being in an inter-pandemic stage, nations plan for pandemic contingency following recommendations of the WHO. National influenza preparedness plans are constantly being refined, aiming to mitigate the effects of pandemic influenza on a national, regional and local level. Even in the absence of a pandemic strain, seasonal influenza causes substantial morbidity and mortality. Seasonal outbreaks put pressure on general practitioners and strain hospital resources, leading to bottlenecks in outpatient treatment and hospital admission capacities.

Various intervention strategies reduce the impact of influenza on individuals and public health systems. In inter-pandemic phases, vaccination is the most important tool to reduce morbidity and mortality, but a potent vaccine will probably not be generally available in the initial phase of a pandemic. Other control strategies like pharmaceutical (antiviral) and non-pharmaceutical interventions (reduction of contact rates) will have to be implemented.
The use of antiviral drugs during a pandemic seems to be the treatment of choice at present\textsuperscript{6,36,52,53}, but not all countries can afford stockpiling enough drugs. Furthermore, concerns about the over-reliance of a "pharmaceutical solution" have been expressed\textsuperscript{54}. An epidemic can also be mitigated by reducing contact rates in the general population and by decreasing the infectivity of cases\textsuperscript{6}. Such reductions can be achieved by measures like quarantine and case isolation\textsuperscript{55}, closing day care centres and schools\textsuperscript{56,57}, cancelling mass gathering events, voluntary self isolation and general behavioural changes in public and increasing social distance\textsuperscript{51}.

The effectiveness of such interventions depends on various factors which must be prospectively explored by sensitivity analyses, based on mathematical models. Here, we use the freely available Java applet \textit{Influsim}\textsuperscript{58} to investigate how effectively pharmaceutical and non-pharmaceutical interventions contribute to mitigate an influenza pandemic while vaccines are not available. In particular, we examine how intervention delays\textsuperscript{59} determine the course of a pandemic and constrain the success of interventions.

1.2. Methods

\textit{Influsim} is a deterministic compartment model based on a system of over thousand differential equations which extend the classic SEIR model by clinical and demographic parameters relevant for pandemic preparedness planning. Details of the simulation and a discussion of the standard parameter values have been described previously\textsuperscript{58}, a summarizing graph of the model is provided in Figure 1.

Figure 1. Model structure of Influsim 2.0. Transitions from each compartment depend on age; transitions from the exposed (E) state into diseased states (A, M, V, X) additionally depend on the risk group which is assigned to susceptible (S) individuals at birth. Other states: W: cases who withdraw at home, H: hospitalized cases, I: recovered and immune individuals, R: individuals in the stage of convalescence, and D: death.
The program and its source code are publicly available to offer transparency and reproducibility. The simulation produces time courses and cumulative numbers of influenza cases, outpatient visits, applied antiviral treatment doses (neuraminidase inhibitors), hospitalizations, deaths and work days lost due to sickness, all of which may be associated with financial loss. The analyses presented here are based on InfluSim 2.0, using demographic and public health parameters which represent the situation in Germany in 2006. Interventions include antiviral treatment, isolation of patients, social distancing measures and the closing of day care centres and schools as well as cancelling mass gathering events.

Using the standard set of InfluSim parameters, about one third of all infected individuals is expected to become severely ill and to seek medical help. Patients seeking medical help will be referred to as “outpatients” throughout this paper. An exponential distribution is used to model the delay between onset of symptoms and seeking medical help; on average, patients visit a doctor after 24 hours. If a patient seeks medical help within 48 hours after onset of symptoms, he or she is given antiviral treatment unless the stockpile of antivirals is exhausted. Antiviral treatment reduces the duration and degree of infectivity of the case and the number of hospitalizations. For more detailed descriptions see 58,61.

Non-pharmaceutical interventions examined in this paper are contact reduction measures and the isolation of cases. The latter effectively leads to reduced contact rates between individuals, too. In the scenarios presented below, we assume that everybody in the population avoids a given percentage of contacts (e.g. by improved hygiene, wearing masks, or behavioural changes) and that sick patients are isolated which reduces the contact rates of moderately sick, severely sick (but non-hospitalized) and hospitalized cases by 10%, 20% and 30%, respectively.

1.3. Results

Assuming a basic reproduction number of \( R_0 = 2.5 \) and using the standard parameter set of InfluSim 58, an epidemic in a population of 100,000 individuals reaches the peak about 40 days after introduction of the infection and is practically over three weeks thereafter if no interventions are performed (Figure 2). During the whole epidemic, 87% of the population become infected, 29% seek medical help, 0.7% are hospitalized and 0.2% die. Figure 2 shows how pharmaceutical and non-pharmaceutical interventions can mitigate this scenario. Contact reduction by isolation of cases alone 61, protracts the peak of the epidemic by about one week. Distribution of antivirals or additional contact reduction measures delay the epidemic by approximately 10 days and are hardly sufficient to provide a substantial delay. A combination of antiviral treatment, isolation of cases and social distancing in the general population seems to be necessary to delay the epidemic in the order of weeks. This example furthermore shows that an efficient mitigation of the epidemic is not necessarily associated with a significant reduction in the number of infections. For information on the proportions of infected people and outpatients see the legends to the Figures.
Figure 2. Comparison of different intervention schemes. Number of outpatients expected during a pandemic wave in a population of 100,000 citizens. Parameter values are based on the InfluSim standard configuration\(^5\) with \(R_0=2.5\), except those listed at the end of this legend and indicated by superscripts\(^1\). The dashed line represents an epidemic without intervention\(^2\). For the following four scenarios, interventions are initiated when infection is introduced (day 0). Isolation: moderately sick, severely sick and hospitalized cases are isolated\(^3\). Treatment: antivirals are available for 10% of the population and all severe and extremely sick cases receive antiviral treatment\(^4\). Under this intervention scheme, antivirals are used up on day 50. Contact reduction: involves isolation\(^3\) of cases and social distancing\(^5\).

All interventions: combination of all three interventions\(^6\); under this intervention scheme, antivirals are used up on day 76, leading to a plateau in the epidemic curve. \(^1\): Parameter modifications are given in the following and terms in italics refer to terms in the InfluSim user interface. InfluSim output: \(N_i\)=cumulative proportion of the population infected, and \(N_o\)=cumulative proportion of outpatients in the population. \(^2\): yielding \(N_i=87\%\), \(N_o=29\%\). \(^3\): Moderately sick cases: 10%, Severe cases (home): 20%, Severe cases (hospital): 30%, yielding \(N_i=81\%\), \(N_o=27\%\). \(^4\): Antivirals availability: 10%, Treatment fraction: 100% for both, Treatment of severe cases and Treatment of extremely sick cases, yielding \(N_i=82\%\), \(N_o=27\%\). \(^5\): General reduction of contacts: Contact reduction by 10%. Combined with isolation of cases, this intervention scheme yields \(N_i=75\%\), \(N_o=25\%\). \(^6\): yielding \(N_i=66\%\), \(N_o=22\%\).

**Intervention with Antivirals**

The mitigating effect of antivirals strongly depends on the onset of their distribution (Figure 3). Antivirals can delay the epidemic if distributed very early while few cases exist in the population. Late distribution of antivirals (e.g. starting on day 30) leads to the paradoxical effect that the stockpile is exhausted even quicker compared to early distribution (shaded areas under the curves in Figure 3). Additionally, the mitigating effect of the intervention drastically diminishes and benefits are restricted to lowering the peak of the epidemic. Unrestricted availability of drugs (grey curves in Figure 3) still leads to an epidemic because (i) asymptomatic and moderately sick cases are not eligible for treatment, (ii) patients visit a doctor on average 24 hours after onset of symptoms while already being highly infectious and (iii) antivirals cannot fully prevent infectivity.

Figure 4 extends these considerations by showing epidemic curves where all clinically ill patients are treated with antiviral drugs until the stockpile is exhausted. The mitigating effect of antiviral distribution is weakly influenced by the amounts of available antivirals, but is strongly determined by the onset of administration. The model suggests that even a small stockpile of antivirals can protract the peak of the epidemic if distributed very early while few cases exist in the population (Figure 4A). In contrast, the mitigating effect becomes negligible, if antivirals are distributed with delay (Figure 4B). Independent of the delay in the distribution of antivirals, their quantitative availability affects only the height of the peak of the epidemic, but hardly the mitigation of the epidemic (Figure 4A, B). For considerations into the final size of the epidemic see below. In summary, delaying the epidemic depends on early action, whereby lowering the peak depends on the quantitative availability of antivirals.
Figure 3. Onset and sustainability of antiviral intervention. Number of outpatients expected during a pandemic wave, varied by day of onset when antivirals come into operation. Parameter values are based on the InfluSim standard configuration with $R_0=2.5$, except those listed at the end of this legend and indicated by superscripts. The dashed curve shows the epidemic without intervention. Antivirals are available for 5% of the population (grey lines), compared to scenarios of full coverage (green lines). The shaded areas under the curves represent the amounts of antivirals distributed and are identical for both scenarios. They are shown between onset of intervention and exhaustion. If antivirals are available at the beginning of the epidemic ("Intervention from day 0") they last for 45 days. Antivirals last only for a shorter period, if coming into operation in later phases of the epidemic ("Intervention from day 30"). Parameter modifications are given in the following and terms in italics refer to terms in the InfluSim user interface. InfluSim output: $N_i$=cumulative proportion of the population infected, and $N_o$=cumulative proportion of outpatients in the population. 1: Yielding $N_o=87\%$, $N_i=29\%$. 2: Antiviral availability: 5\%, Treatment fraction: 100\% for both, Treatment of severe cases and Treatment of extremely sick cases, yielding $N_o=84\%$, $N_i=28\%$ for scenarios, "day 0" and "day 30". 3: Antiviral availability: 100\%, Treatment fraction: 100\% for both, Treatment of severe cases and Treatment of extremely sick cases, yielding $N_o=72\%$, $N_i=24\%$ for "day 0" and $N_o=74\%$, $N_i=25\%$ for "day 30". 4: Antiviral availability: 5\%, Treatment fraction: 100\%, Range of days: 0-80 for both, Treatment of severe cases and Treatment of extremely sick cases. 5: Antiviral availability: 5\%, Treatment fraction: 100\%, Range of days: 30-80 for both, Treatment of severe cases and Treatment of extremely sick cases.

Figure 4. Intervention with limited amounts of antivirals. Number of outpatients expected during a pandemic wave, varied by the availability of antivirals. Parameter values are based on the InfluSim standard configuration with $R_0=2.5$, except those listed at the end of this legend and indicated by superscripts. Antiviral availability ranges from 0% (no antivirals available, dashed curves) to 10% (antivirals available for 10% of the population) in steps of 1% (from left to right). The dashed curve shows the epidemic without intervention. Grey dotted lines represent the scenario where antivirals are available for the whole population. Bars at the bottom of each graph indicate the period when antiviral treatment begins (model input) until stockpiles are used up (model output). A: Antivirals are available from day 0. B: Antivirals become available after three weeks. The epidemic curves depart from the grey dotted line when antivirals are exhausted. Parameter modifications are given in the following and terms in italics refer to terms in the InfluSim user interface. InfluSim output: $N_i$=cumulative proportion of the population infected, and $N_o$=cumulative proportion of outpatients in the population. 1: Antiviral availability: 0%, yielding $N_o=87\%$, $N_i=29\%$ for both, A and B. 2: Antiviral availability: 10%, yielding $N_o=82\%$, $N_i=27\%$ for both, A and B. 3: Antiviral availability: 50%, yielding $N_o=72\%$, $N_i=24\%$ for both, A and B. 4: Range of days: 0-80. 5: Range of days: 21-80.
**Intervention through contact reduction**

Contact reduction measures, comprising social distancing and the isolation of cases, can be an effective part of mitigation strategies; they have the advantage over antiviral treatment to be not limited *per se*, i.e. they can be continued for a sufficiently long period of time. Figure 5 examines the effect of isolation of cases and social distancing measures (see figure caption for details) in the absence of antiviral treatment. The peak of the epidemic is protracted by about 1 day for every percent of contact reduction if this intervention starts immediately after the introduction of the infection. Thus, a peak shift is not only possible by early action, but also by the degree of contact reduction. If contact reduction is initiated later, the peak shift diminishes, but the proportionality remains. For example, if the intervention starts three weeks after the introduction of infection, the peak of the epidemic is only mitigated by about half a day per 1% contact reduction (Figure 5B). Premature cessation of contact reduction measures restores the infection rates to the pre-intervention values which fuels the epidemic. It can lead to a delayed course and a higher total number of infections, involving a plateau or even a second peak of the epidemic (Figure 5C).

**Figure 5.** Effects of contact reduction measures. Number of outpatients expected during a pandemic wave if contact reduction measures are implemented additionally to the isolation of cases. Parameter values are based on the *Influsim* standard configuration with $R_0=2.5$, except those listed at the end of this legend and indicated by superscripts. The dashed curve shows the epidemic without intervention. Contact reduction involves social distancing and isolation of cases. The curves show the effects caused by social distancing, where contacts are reduced by 0% (grey curve) up to 30% in steps of 2% (black curves, from left to right). Bars at the bottom of each graph illustrate the periods of contact reduction, which are in A: full, from day 0 to end, in B: delayed, from day 20 to the end, and in C: temporarily, from day 20 to day 50. Parameter modifications are given in the following and terms in italics refer to terms in the *Influsim* user interface. *Influsim* output: $N_i=$cumulative proportion of the population infected, and $N_o=$cumulative proportion of outpatients in the population. Contact reduction: ranging from 0-30% in steps of 2%. Range of days: varied between A, B, and C, see legend or grey bar at the bottom of each graph. Isolation: Moderately sick cases: 10%, Severe cases (home): 20%, Severe cases (hospital): 30%. Range of days: varied between A, B, and C, see legend or grey bar at the bottom of each graph. Intervention effect is based on *Isolation* alone, yielding $N_i=81\%$, $N_o=27\%$ in A, B and C. Yielding in A: $N_i=56\%$, $N_o=19\%$, and B: $N_i=57\%$, $N_o=19\%$, and C: $N_i=82\%$, $N_o=27\%$. 

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Figure 5A: Outpatients per 100,000 vs. Days

Figure 5B: Outpatients per 100,000 vs. Days

Figure 5C: Outpatients per 100,000 vs. Days
**Figure 6.** Combined intervention scheme. Number of outpatients expected during an influenza pandemic if antiviral distribution and contact reduction measures are implemented additionally to the isolation of cases. Parameter values are based on the InfluSim standard configuration with $R_0=2.5$, except those listed at the end of this legend and indicated by superscripts. The Figure shows the epidemic curves, varied by the "Day when contact reduction measures are initiated" (as indicated by the number next to the peak and at the right hand side of the bar chart). Antivirals are available for 10% of the population and are distributed from day zero. Contact reduction measures involve isolation of cases and social distancing. Bars at the bottom of the graph illustrate begin and end antiviral intervention (dark bars) and contact reduction measures (light bars), respectively. The "Day when contact reduction measures are initiated" is model input, whereas the "Day when antivirals are used up" is model output. The epidemic without intervention is shown as a dashed curve. The curves for "7", "21", "35" and "49" are plotted in bold for purposes of visualization. Parameter modifications are given in the following and terms in italics refer to terms in the InfluSim user interface. InfluSim output: $N_i$=cumulative proportion of the population infected, and $N_o$=cumulative proportion of outpatients in the population. Antiviral availability: 10%. Treatment fraction: 100%, for both. Treatment of severe cases and Treatment of extremely sick cases. Moderate sick cases: 10%, Severe cases (home): 20%, Severe cases (hospital): 30%. Range of days: see bar chart at the bottom of the graph. For "day 0", $N_i=53\%$, $N_o=18\%$. For "day 28": $N_i=55\%$, $N_o=18\%$, for "day 42": $N_i=60\%$, $N_o=20\%$, for "day 49": $N_i=69\%$, $N_o=23\%$. Combined intervention scheme

The preceding examples with interventions based on antivirals or contact reduction alone yielded peak delays only in the order of weeks, whereas months may be required for vaccine development and production demand-
ing for a combined intervention scheme (Figure 6). We examine an optimistic scenario where antivirals are distributed immediately after the infection is introduced (dark bars in Figure 6), while varying the onset of social distancing measures. The antiviral stockpile lasts longer if social distancing measures are initiated earlier (pale bars in Figure 6). Immediate initiation of contact reduction can protract the epidemic by months, whereas a delayed initiation leads to a plateau in the epidemic curve at a time when antivirals are used up.

**Cumulative number of infections and outpatients**

Without interventions, $N_i=87\%$ of the population become infected during the course of the epidemic and the cumulative number of outpatients reaches $N_o=29\%$, reflecting the assumption that approximately one third of infected individuals becomes sufficiently sick to seek medical help. These outcomes remain surprisingly stable even for interventions assuming optimistic resources (cf. footnotes to Figures 1-5). For instance, immediate and unlimited availability of antivirals reduces these fractions only to $N_i=72\%$ and $N_o=24\%$ (Figure 3). This minor effect has three reasons: only about one third of cases seek medical help and will receive antiviral treatment, many infections are passed on before cases seek medical help and antiviral treatment does not fully prevent further transmission. These disadvantages do not apply to contact reduction measures. For instance, a reduction of 20% of contacts reduces these fractions to $N_i=68\%$ and $N_o=22\%$ (Figures 4A, B). A combination of antiviral treatment and contact reduction can further reduce these values to $N_i=53\%$ and $N_o=18\%$ (Figure 6).

**Uncertainty in the parameter values**

In the preceding analyses it was assumed that parameter values are precisely known; in a real world scenario, however, uncertainty arises from biological variability, stochastic influences, heterogeneities, etc. We illustrate with a concluding example to which extent simulated epidemics are affected by uncertainty in the parameter values. As shown in Figure 7, epidemics can be highly variable, although only four parameters have been varied within moderate ranges. Varying more parameters would further increase this variability.

For the interventions and parameter variations considered, the cumulative number of outpatients ranges from a few thousand to over twenty thousand (see inset in Figure 7). Among the four parameters, $R_0$ is the strongest predictor of the number of outpatients (analysis not shown) as it strongly determines how quickly antivirals become exhausted. In two out of 1,000 simulations the randomly chosen parameter combinations involved values for $R_0$ around 1.8 which led to very minor outbreaks given the intervention scheme. The cumulative number of outpatients escalates when antiviral stockpiles become exhausted while the proportion of susceptibles is still large enough to allow for further propagation of infectives. In this case, the epidemic curve proceeds with a second wave or a plateau.
Figure 7. Sensitivity analysis considering uncertainty of parameter values. Variability in epidemic curves (large plot) and the distribution of the cumulative number of outpatients (inset), originating from the uncertainty in four parameters (right panel). Parameter values are based on the InfluSim standard configuration with $R_0=2.5$, except those listed at the end of this legend and indicated by superscripts. The sensitivity analysis extends the scenario shown in Figure 6, where antivirals are available for 10% of the population and are distributed from day zero, and where contact reduction measures, including the isolation of cases, are initiated three weeks after the introduction of infection (scenario “day 21”). Right panel: parameter values for each realization are sampled independently from normal distributions as shown (means given in bold, 99% of the values lie within the range specified by dotted lines, except $b_A$ which is truncated). $R_0$: basic reproduction number, $x_{50}$: cumulative infectivity during the first half of the symptomatic period, $b_A$: relative infectivity of asymptomatic cases, $f_c$: antiviral treatment reduces infectivity by a factor of $1-f_c$. For each parameter, an increase of the value aggravates the epidemic. Large plot: from a hundred random realizations, we selected the two most extreme epidemics, and eight epidemics homogeneously placed between them. The epidemic with $N_0=20800$ is caused by parameter values drawn from the left tail of the corresponding distributions, and the epidemic with $N_0=5000$ is caused by parameter values drawn from the right tail of the corresponding distributions (see right panel). The epidemic curves show a plateau or a second wave when antiviral stockpiles are exhausted while the proportion of susceptibles is still large enough to allow for further propagation of infectives (thin curves in black); for optimistic parameter combinations (e.g. small $R_0$), the available stockpiles last over the whole period of the intervention and the epidemic curve proceeds without a plateau (bold curves in grey). Inset: distribution of cumulative number of outpatients obtained from 1,000 random realizations. $^1$: Parameter modifications are given in the following and terms in italics refer to terms in the InfluSim user interface. $^2$: Antiviral availability: 10%. Treatment fraction: 100%, for both, Treatment of severe cases and Treatment of extremely sick cases. $^3$: Contact reduction by: 20%. Range of days: day 21-360. $^4$: Moderately sick cases: 10%, Severe cases (home): 20%, Severe cases (hospital): 30%. Range of days: day 21-360.
1.4. Discussion

With pandemic influenza, we have to “expect the unexpected”\(^6\). Historical reports frequently mention the surprising speed at which a pandemic wave travels through the population\(^63-65\). Predicting the course of a future pandemic caused by a virus with unknown characteristics is based on substantial uncertainties and we must rely on sensitivity analyses, performed with mathematical models like \textit{InfluSim}.

Because of the short serial interval of influenza, timely action is essential. Different control measures must be regarded as complementary and not as competing. Neither antiviral treatment nor non-pharmaceutical measures should be used exclusively to mitigate a pandemic influenza wave.

\textit{Antivirals}

Infectious disease models have suggested that an upcoming influenza epidemic with a low basic reproduction number might be contained at the source through targeted use of antiviral drugs\(^6,38\). The published scenarios concern WHO phases 4 and 5 ( interpandemic alert period) and assume that an outbreak starts in a rural area with low population density. It can be expected that the pandemic virus will be introduced into Europe and the US after a local epidemic (i.e. in WHO phase 6). Community-based prophylaxis, however, is of limited use for several reasons. Under a high prevalence of infection in phase 6, a wide distribution requires an enormous number of antiviral courses; with available stockpiles, it will be virtually impossible to locally contain the pandemic with targeted antiviral prophylaxis. Development of resistance, limited production capacities and extremely high costs are further limitations of this strategy, so that population-wide prophylaxis has not been recommended by the WHO for the final phase of the pandemic\(^44\).

The discussion of pandemic influenza preparedness planning has frequently focussed on the amounts of drugs to be stockpiled and to whom and when they should be supplied\(^66\). Even if the currently stockpiled antiviral drugs will be fully effective against the pandemic strain, their use may not be able to sufficiently prevent the spread of influenza because (i) transmission of the infection may occur before the onset of clinical symptoms (as assumed in the \textit{InfluSim} model)\(^67\), (ii) asymptomatic\(^68\) and moderately sick cases\(^49\) are usually not treated despite contributing to transmission, and (iii) the occurrence of cases with influenza-like illness caused by other pathogens may lead to an accelerated depletion of the antiviral stockpile. Likewise, moderately sick cases or even healthy people may seek medical help and succeed in receiving antiviral treatment which would further deplete the stockpile. These factors reduce the efficacy of pharmaceutical control measures\(^69\), indicating the demand of extending this strategy by non-pharmaceutical intervention measures.

Especially if antivirals are limited, they should be supplied as early as possible. If their distribution is delayed, cases become so abundant that resources will quickly be exhausted without having much impact on the spread of the disease (Figures 2 and 3). This confirms that the amount of antivirals needed strongly depends on the number of infections that are present when the intervention is initiated\(^70\). If antiviral drugs are extremely limited, they should be used to preferably treat severe cases that need hospitalization. Although this has practically no effect on the pandemic wave \textit{per se}, it helps to reduce the death toll in the population (results not shown).
**Contact reduction**

Rather than relying on a pharmaceutical solution, pandemic preparedness should also involve non-pharmaceutical measures (see above). Early self-isolation and social distancing measures can be highly effective, as shown for the SARS epidemic\(^71\): after the WHO’s global alert and the implementation of massive infection control measures, the effective reproduction numbers in Hong Kong, Vietnam, Singapore and Canada fell below unity. Rigorous social distancing measures in the entire population, however, will tax the social and economic structure and the population may not be willing or able to reduce contacts during the whole course of a pandemic wave.

For Figure 6, we assumed that contact reduction measures (e.g. improved hygiene, wearing masks, or behavioural changes) could add up to reduce contacts by 20%. Studies on the SARS outbreak suggest some preventative effect of wearing masks\(^72-74\), but compliance, availability of masks and their effectiveness against influenza infection remain unknown factors. Stockpiling surgical masks for the population results in exorbitant high numbers and may not be feasible\(^14\) and individual stockpiling may be impossible due to economic limitations, especially in crisis situations. Since the specific effects of such behavioral changes remain uncertain, we modeled their contribution as a general reduction in contact rates.

In contrast to SARS, we will not be able to rely on isolating hospitalized cases when a new influenza pandemic emerges. Using the standard parameter settings of InfluSim, we expect only a total of 0.7% of the population to be hospitalized. Even for the worst case scenario of the US Pandemic Preparedness Plan, where this value may be up to ten times larger\(^75\), the wide majority of infected individuals is never hospitalized. With influenza, we have to rely on self-isolation of moderately sick cases and of bed-ridden patients who stay at home. As these cases form the majority of infections and exert the highest force of infection, even a moderate reduction of contacts between them and the general population can substantially change the pandemic wave.

**Conclusions**

Time is of the essence when controlling infectious diseases that spread at high speed and thus, interventions are most effective in the beginning when only few people are infected. Only a timely application of antiviral drugs (even with limited supplies) and a quick implementation of contact reduction measures will notably protract the peak of the epidemic and substantially reduce its height. Whereby the protraction of the pandemic wave is essential, it is the height of the peak of a pandemic wave which can easily overtax general practitioners as well as hospitals and whole public health systems, and can lead to dangerous bottlenecks in basic and emergency medical care. Vaccinating a small fraction of the population would have a similar effect on the course of the epidemic as reducing the basic reproduction number by the percentage of immunized individuals (e.g. by 10%).

The sensitivity analyses at the end of the Results section shows that the planning of intervention strategies must not only be based on single parameter values, but must also address their variability. Mathematical models like InfluSim should not only be used to predict a specific outcome, but also to explore best and worst case scenarios.
1.5. Appendix: brief description of InfluSim

For a detailed description of InfluSim see \[^{56}\].

General description

InfluSim is a deterministic compartment model based on a system of over 1,000 differential equations which extend the classic SEIR model by clinical and demographic parameters relevant for pandemic preparedness planning. It allows for producing time courses and cumulative numbers of influenza cases, outpatient visits, applied antiviral treatment doses, hospitalizations, deaths and work days lost due to sickness, all of which may be associated with economic aspects. The software is programmed in Java and open access \[^{60}\], it operates platform independent and can be executed on regular desktop computers.

Model description

The model structure of InfluSim is represented by Figure 7, with descriptions given below.

![Model structure of InfluSim 2.0. Transitions from each compartment depend on age; transitions from the exposed (E) state into diseased states (A, M, V, X) additionally depend on the risk group which is assigned to susceptible (S) individuals at birth. Other states: W: cases who withdraw at home, H: hospitalized cases, I: recovered and immune individuals, R: individuals in the stage of convalescence, and D: death.](image-url)
Natural history of disease

Susceptible individuals (S) are infected at a rate which depends on their age and on the interventions applied at the current time. Infected individuals (E) incubate the infection for a mean duration of 1.9 days. As predictions depend on assuming realistic distributions for transitions, the incubation period is modelled in 7 stages yielding a gamma distributed incubation period with a coefficient of variation of 37.8%. The last 2 incubation stages are regarded as early infectious period during which patients may already spread the infection. This accounts for an average time of about half a day for the standard set of parameters.

After passing through the last incubation stage, infected individuals become fully infective and a fraction of them develops clinical symptoms (Figure 8A). The course of disease depends on their age and risk group: one third remains asymptomatic (A), one third shows a moderate course of disease (M, "moderately sick") and the remaining third a severe course of disease (V, "very sick"); a small fraction of the latter third shows an extremely severe course of disease (X, "extremely sick") and needs hospitalization. The rationale for distinguishing extremely sick cases is that only these can die from the disease and need to be hospitalized; in all other aspects, both groups of severe cases are identical. The period of infectivity is gamma distributed and depends on the course of the disease and on the age of the case. To allow for an infectivity which changes over the course of disease, we apply weighting factors which depend on the stage of infectivity. Our standard value results in an infectivity which is highest immediately after onset of symptoms and which declines in a geometric progression over time (Figure 8B).

Figure 8. Time-course of symptoms and infectivity. Symptoms and infectivity dependent on time, for cases with a severe (V), a moderate (M) or an asymptomatic (A) course of disease (treatment is indicated by subscripts). A: Fraction of symptomatic cases among all cases by time since infection. B: Relative infectivity by time since infection (given in arbitrary units, as the probability of transmitting the infection also depends on the age-dependent probability of meeting other people as given by the contact matrix).

Severe cases seek medical help on average one day after onset of symp-

toms, whereby the waiting time until visiting a doctor is exponentially dis-
tributed. Very sick and extremely sick patients who visit a doctor may be offered antiviral treatment. Very sick patients are advised to withdraw to their home (W) until the disease is over whereas extremely sick cases are immediately hospitalized (H). Death rates of extremely sick and hospitalized cases are age-dependent. Whereas asymptomatic and moderately sick patients who have passed their duration of infectivity are consid-
ered healthy immunes, very sick and extremely sick patients first become convalescent before they resume their ordinary life (gamma distributed with a mean of 5 days and coefficient of variation of 33.3%). Fully recovered patients who have passed their period of convalescence join the group of healthy immunes; working adults will return to work, and children again visit day care centres or schools.

**Interventions**

Antiviral treatment: Severe and extremely severe cases who visit the doctor within at most two days after onset of symptoms are offered antiviral treatment, given that its supply has not yet been exhausted. Antiviral treatment reduces the patients’ infectivity by 80 percent, the duration of being diseased by 25%, and the risk of hospitalization by 50 percent. Extremely sick patients, whose hospitalization is prevented by treatment, are sent home and join the group of treated very sick patients.

Social distancing measures: Contact rates in the general population can be reduced by increasing “social distance”, by closing schools and day care centres, by cancelling mass gathering events, or by behavioural changes.

Isolation of cases: Isolation of cases reduces their contact rates. Contacts are not necessarily reduced by 100%, but between 0 and 100%, as specified by the user. Our standard scenario considers reductions of 10%, 20% and 30% for moderately sick cases, very sick cases (at home) and extremely sick cases (hospitalized), respectively.

**Mixing matrix, basic reproduction number and force of infection**

For the mixing of the age classes, we employ a "who-acquires-infection-from-whom matrix" (WAIFW matrix) which gives the relative frequency of contacts of infective individuals by age. *Influsim* assumes bi-directional contacts (e.g. children have the same total number of contacts with adults as adults with children). In order to match the user-specified basic reproduction number $R_0$, the disease-specific infectivity and the durations of infectivity in this matrix must be incorporated, resulting in the next generation matrix. This matrix is multiplied with a scaling factor chosen such its largest eigenvalue is equal to the chosen value of $R_0$. The force of infection is given as the product of the number of infective individuals and the corresponding age-dependent contact rates.

**Initial values**

At the start of the simulation, one infection is introduced into the fully susceptible population. To avoid bias between simulations, the initial infection is distributed over all age and risk classes.
2. Stochastic approach:
Contact structures in the population determine the efficacy of antiviral drugs to control an influenza pandemic

Planning adequate public health responses against emerging infectious diseases requires predictive tools to evaluate the impact of candidate intervention strategies. With current interest in pandemic influenza very high, modeling approaches have suggested antiviral treatment combined with targeted prophylaxis as an effective first-line intervention against an emerging influenza pandemic. To investigate how the effectiveness of such interventions depends on contact structure, we simulate the effects in networks with variable degree distributions. The infection attack rate can increase if the number of contacts per person is heterogeneous, implying the existence of high degree individuals who are potential super-spreaders. The effectiveness of a socially targeted intervention suffers from heterogeneous contact patterns and depends on whether infection is predominantly transmitted to close or casual contacts. Our findings imply that the various contact networks’ degree distributions as well as the allocation of contagiousness between close and casual contacts should be examined to identify appropriate strategies of disease control measures.

2.1. Introduction

Understanding disease transmission and controlling disease outbreaks are primary public health objectives. The threat of emergent and re-emergent diseases, such as SARS and pandemic influenza, has made the research community and the general public more aware of the need for accurate and robust planning tools. Among these tools, individual-based computer simulations are important for allowing explicit consideration of contact structures in the population. Contact structures are the basis for the transmission of the infection, but they must be regarded as highly disease-specific and may remain unknown for many diseases. In these cases, model-based evaluations of competing intervention schemes must be subject to sensitivity analyses across varying networks.

With current interest in pandemic influenza very high, massive computer simulation models have been used to investigate optimal intervention strategies, and a promising intervention approach against emerging pandemic influenza is the distribution of antivirals based on geographic proximity and/or contact patterns\cite{6,38}. Intervention strategies that rely on contact information are affected by the network structure and various investigations have shown that disease dynamics and intervention effectiveness depend on the type of the contact network \((\text{e.g. } 13,14,16,18,77-81)\).

Networks can be characterized by various measures, but epidemiological phenomena can often be sufficiently explained by the average degree\cite{20}, i.e. the average number of contacts per person. If, however, contacts in the population are highly dispersed, the infection dynamics may no longer be well characterized by the average degree\cite{82}. Measures based on the variance and/or the skewness of the degree distribution\cite{83} are then more appropriate, because they give more
weight to the individuals who infect a disproportionately large numbers of other individuals. These so-called super-spreaders can introduce substantial stochasticity into the course of an epidemic, because their impact on the epidemic curve strongly depends on when they are involved in transmission. Scale-free networks, whose skewed degree distributions allow for the existence of highly connected individuals, are therefore potentially relevant for network epidemiology.

Scale-free networks show observed characteristics which cannot be reproduced by other types of networks. Conclusions based on network studies, however, take place in a situation of uncertainty as they examine only a certain collection of networks. In infectious disease epidemiology, scale-free contact networks have to date been only described for sexual relationships. The actual contact network involved in transmission of airborne diseases is difficult, perhaps impossible, to establish, but weakly skewed or even normal degree distributions have been suggested. Taken together, this means that networks generated by a preferential attachment scheme that can produce a range of degree distributions might be candidates for studies in the field of network epidemiology.

To model diseases in which transmission rates or risks differ between casual and close contacts (within-household contacts), the network structure must distinguish between these two groups. For influenza, there is no consensus as to whether infection is predominantly transmitted via close or casual contacts, because it seems to depend on the strain involved, or at least be different for seasonal and pandemic influenza. One would expect that the effectiveness of targeted interventions and prophylaxis schemes depends on how the overall basic reproduction number \((R_0)\) is distributed between these two groups. Sensitivity analyses addressing this issue have so far not been performed.

The aim of this study is to investigate how the final size of an epidemic and the effectiveness of intervention depend upon network structure and the relative contagiousness of close and casual contacts, using a model of pandemic influenza and antiviral treatment combined with targeted prophylaxis. We explore these effects in networks which are based on preferential attachment, but allow for tunable degree distributions. Dispersion of the degree distribution is represented by its standard deviation (which is strongly determined by the degree of individuals with many contacts) and by the average clustering coefficient (describing to what extent people within neighbourhoods are in contact with each other). Our results help to identify uncertainties of interventions in real social networks and emphasize the relevance of projects that investigate the structure of such networks.

### 2.2. Methods

**Network**

A simulated closed population of 10000 individuals was created and individuals in the population were assigned both close (household) contacts and casual (any other) contacts. For the close contacts, the population was partitioned into households whose sizes were chosen from a distribution...
of household sizes in Thailand, which has been regarded as a potential country of origin of pandemic influenza with detailed demographic data. Everyone in a household was assumed to be in close contact with all other individuals in the household. The minimum, maximum and average household size is $H_{\text{min}} = 1$, $H_{\text{max}} = 10$ and $\overline{H} = 3.57$, respectively. The average number of close contacts in the network equals then $\overline{D}_h = \sum_{i=1}^{H_{\text{max}}} (i-1)f_i = 3.13$, where $N$ is the population size and $f_i$ is the relative frequency of individuals who live in a household of size $i$.

The network for casual contacts was created using a generalization of the Barabási-Albert scale-free network generation algorithm (Barabási & Albert, 1999) in which a tuning distribution is used to alter the preferential attachment scheme, yielding degree distributions that can vary from that of the scale-free network. In the classical preferential attachment procedure, the tuning distribution is uniform, yielding a degree distribution of the power law type which is represented by a straight line on log-log scale. The tuning distributions used for this investigation were beta distributions which allow for modifying the shape of the degree distribution in a flexible way, as illustrated in figure 1. The algorithm for the network of casual contacts starts with eight individuals who are connected as a ring, implying two casual contacts per individual (remaining contacts, see below). Network growth proceeds by subsequently adding new individuals who always establish four casual contacts to individuals of the existing network by the modified preferential attachment scheme. After the last individual has been added, the remaining contacts for the initial ring of individuals were completed, using the modified preferential attachment scheme, too. The minimum degree of $D_{\text{min}}=4$ results in those cases when an individual has only these four casual contacts and no close contacts. In order to test the sensitivity of our results to the initial ring configuration of individuals, networks were generated beginning with a complete graph on the initial individuals. Conclusions in this investigation do not depend on this initial configuration.

![Figure 1](image-url)  
**Figure 1.** Examples of degree distributions of different networks with increasing standard deviation (SD) in a population of 10000 individuals. The unimodal structure in the low-degree region originates from close contacts within households. All networks have an average degree of 3.13 close and 8 casual contacts. The distributions were generated using the algorithm described in with no extra clustering ($c=0$) and beta tuning distributions with parameter values: (a): $\alpha=1.4$, $\beta=0.7$, (b): $\alpha=1.4$, $\beta=1.0$, (c): $\alpha=1.0$, $\beta=1.2$.  

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Heterogeneity in the degree distributions of all contacts (close and casual) is represented by the standard deviation (SD). The above mentioned household structure of close contacts combined with a classic scale-free network of casual contacts yields degree distributions with $SD_{SF} \approx 10.8$. A degree distribution will be called underdispersed if $SD < SD_{SF}$ and overdispersed if $SD > SD_{SF}$. In general, the SD is highly influenced by outliers, given in this context by $D_{\text{max}}$, the maximum degree of the degree distribution.

Networks with differing standard deviation and clustering were generated from 45 different parameter constellations, originating from nine different beta distributions (all parameter combinations of $\alpha \in \{1.0, 1.4, 2.0\}$ and $\beta \in \{0.7, 1.0, 1.2\}$) and 5 different clustering parameters \(c \in \{0, 0.25, 0.5, 0.75, 1.0\}\). The clustering parameter $c$ is the probability that an individual chooses to connect randomly among the contact persons of his/her current contacts (triad formation step), instead of using the preferential attachment step. The algorithm produced degree distributions with values for the root skewness of $3.2 < SD < 17.2$, maximum degrees of $22 < D_{\text{max}} < 960$ and average clustering coefficients between 0 and 0.5. With 100 simulation repetitions for epidemics with and without intervention, these variations result in $9 \cdot 5 \cdot 100 \cdot 2 = 9000$ total networks used for each of the three scenarios shown in figure 3. Independent of the parameter settings, the network had an average of $D_{c} = 8$ casual contacts and $D_{h} = 3.13$ close contacts yielding an average combined degree of $D = 11.13$.

**Individual-Based Simulation**

The contact network is the basis for a stochastic individual-based simulation of an influenza epidemic. Each network node represents an individual and each edge represents a potential contact along which the infection can spread. Individuals have discrete internal states describing the states of infection, symptoms and treatment. State changes of the individuals are executed in chronological order, using parameters as listed in Table 1. The parameter estimates described in the following paragraphs have been adopted from previous simulation studies\(^4^9,^9^3\).

The infection states are 'susceptible', 'exposed', 'infectious' and 'removed', following the notation of classic SEIR models. Initially all individuals except the index cases are susceptible. Infection is introduced into the population by 10 randomly chosen index cases on day zero. Newly infected individuals enter the latent period, the length of which is assumed to be gamma distributed with mean $T_{L} = 1.6$ days and a coefficient of variation of $CV_{L} = 35\%$. Individuals in the latent period are not yet infectious and show no symptoms. In the subsequent infectious period (gamma distributed with mean $T_{I} = 4.1$ days and $CV_{I} = 23\%$), individuals infect contacts with rate $\beta$ (see next section). Loss of immunity is neglected, as only epidemic (and no endemic) scenarios are investigated.

The symptom states are 'asymptomatic', 'symptomatic' and 'immune' or 'dead'. Symptoms, which are a prerequisite for diagnosis and treatment (see below), appear at the beginning of the infectious period. For influenza we assume that a fraction of $1 - F_{s} = 33\%$ of
infections proceed asymptomatically, and that these individuals are only half as infectious as symptomatic cases (r=50%). We assume that about $F_w=73\%$ of infected and symptomatic cases stay at home, having contact with family members only. The other 27 % of symptomatic cases continue circulating and transmitting the infection to their casual contacts. The symptomatic state ends with the infectious period, after which individuals no longer contribute to transmission as they are either immune or dead.

The treatment states are 'no treatment', 'prophylaxis' and 'treatment'. The intervention scheme is based on antiviral treatment of cases and prophylaxis of their close contacts. Treatment is restricted to the 67 % of infected individuals who show symptoms and we assume a compliance rate of 80 %. Treatment starts one day after the onset of symptoms, is continued for five days and reduces infectiousness by 62 %. Prophylaxis of close contacts (i.e., household members) begins simultaneously with the treatment of the symptomatic family member, but lasts for a period of ten days. Prophylaxis has a compliance of 80 % and reduces the susceptibility of an individual to 30 %.

---

**Population**
- Simulated population size: 10000
- Introduction of infection by 10 index cases, randomly chosen from the population

**Infection**
- Duration of latent period: gamma distributed with mean 1.6 days and CV =35%
- Duration of infectious period: gamma distributed with mean 4.1 days and CV =23%
- Immunity: no loss of immunity
- Fraction of infections that are asymptomatic: $1-F_s=33\%$

**Contagiousness**
- Scenario 1: $\beta_h=0.116$ and $\beta_c=0.058$ contacts per day, yielding an IAR of ≈50%
- Scenario 2: $\beta_h=0.088$ and $\beta_c=0.044$ contacts per day, yielding an IAR of ≈30%
- Scenario 3: $\beta_h=0.047$ and $\beta_c=0.094$ contacts per day, yielding an IAR of ≈50%
- Scenario 4: $\beta_h=0.035$ and $\beta_c=0.070$ contacts per day, yielding an IAR of ≈30%
- Reduction of infectiousness of asymptomatic cases: $r = 50\%$
- Fraction of circulating cases among symptomatic cases: $1-F_w = 27\%$

**Antiviral treatment of cases**
- Duration: 5 days
- Delay: 1 day after onset of symptoms
- Infectiousness under treatment is reduced by 62%

**Antiviral prophylaxis of close contacts**
- Duration: 10 days
- Delay: 1 day after onset of symptoms of a family member
- Susceptibility under prophylaxis is reduced by 70%

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**Table 1**
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
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The infection attack rate (IAR) is determined by the contact rate $\beta$ and is the overall percentage of the population that is infected during the course of the epidemic. CV: Coefficient of variation.
Transmission rates and infection attack rates

Transmission rates were chosen so that baseline epidemics in networks with the highest variance and without intervention cause an infection attack rate (IAR) of either approximately 50% or approximately 30% of the population. Since the distribution of $R_0$ between close and casual contacts is not known, we address by sensitivity analyses two hypotheses: the rate of transmission to close contacts (index $h$) is either twice the rate of transmission to casual contacts (index $c$) ($\beta_h = 2 \beta_c$) or vice versa ($\beta_h = 0.5 \beta_c$). This yields the following four scenarios:

1. Transmission predominantly to close contacts, baseline IAR $\approx 50\%$ ($\beta_h = 0.116$, $\beta_c = 0.058$)
2. Transmission predominantly to close contacts, baseline IAR $\approx 30\%$ ($\beta_h = 0.088$, $\beta_c = 0.044$)
3. Transmission predominantly to casual contacts, baseline IAR $\approx 50\%$ ($\beta_h = 0.047$, $\beta_c = 0.094$)
4. Transmission predominantly to casual contacts, baseline IAR $\approx 30\%$ ($\beta_h = 0.035$, $\beta_c = 0.070$)

Within each scenario, contact rates are kept constant and thus, changes in the IAR are attributable to network structure.

Basic reproduction number $R_0$

We assume that the time until infection is exponentially distributed with mean $1/\beta$ and density $P(t) = \beta e^{-\beta t}$, and the probability that a contact is infected by time $t$ is $\int_0^t P(\tau) d\tau = 1 - e^{-\beta t}$. The expected number of persons who are infected by time $t$ if $m$ persons are in contact with the case is then $S^* = m(1 - e^{-\beta t})$. All $m$ contact persons are infected if the case is contagious forever. Since this is not true, $S^*$ must be weighted with the probability that a case is infectious by time $t$, and we assume the infectious period to be gamma distributed with mean $\mu$ and coefficient of variation $\nu$, thus

$$Q(t) = \frac{e^{-\mu t} t^{\nu-1} \left(\frac{1}{\nu} \mu t \right)^{\nu} \Gamma(\nu)}{\Gamma(\nu + \mu \nu t)}.$$

Weighting $S^*$ with $Q(t)$ yields the expected number of secondary infections,

$$S = \int_0^\infty m(1 - e^{-\beta t})Q(t) d\tau = m \left(1 - \left(\frac{1}{1 + \nu^2 \beta \mu}\right)^{\nu/\mu}\right).$$

(S is lower than the "classical" $R_0$ which does not adequately consider the infectious period, leading to a situation where repeated infections of the same individual are possible and consequently, the spread of the disease is overestimated.)

A model with close and casual contacts involves the two contact rates $\beta_h$ and $\beta_c$, and $m_h$ close and $m_c$ casual contacts. Correspondingly, the expected numbers of secondary infections can be calculated as $S_h$ and $S_c$, and a proxy for the basic reproduction number is their sum, i.e. $R_0 = S_h + S_c$.

With $m_h = 3.11$ close and $m_c = 8$ casual contacts on average, the four scenarios yield the following reproduction numbers:

1. 50% IAR: $S_h = 1.17$, $S_c = 1.68$, yielding $R_0 = 2.85$
2. 30% IAR: $S_h = 0.93$, $S_c = 1.31$, yielding $R_0 = 2.24$
3. 50% IAR: $S_h = 0.54$, $S_c = 2.54$, yielding $R_0 = 3.08$
4. 30% IAR: $S_h = 0.41$, $S_c = 1.98$, yielding $R_0 = 2.39
2.3. Results

Epidemic curves

Figure 2 shows examples of simulated epidemics in networks with high (a) and low (b) dispersion of the degree distribution. Although transmission is driven by the same transmission rates in both networks ($\beta_h=0.088$, $\beta_c=0.044$, see Methods and cf. figure 3b) the course of the epidemics as well as the infection attack rates differ considerably. Epidemics in networks with high variance pervade the population more quickly with more individuals infected compared to epidemics in networks with lower variance.

Highly contagious influenza strains

For highly contagious influenza strains, the size of the epidemic does not depend on heterogeneity in the degree distribution if no intervention is performed (figure 3a). With ten index cases in a population of 10000, major epidemics occur in more than 99 % of simulations, independent of whether infection is predominantly transmitted via close or casual contacts. On the other hand, intervention effectiveness does depend on heterogeneity in the degree distribution and is more efficient in networks with low variance than with high variance (figure 3c and e). Under intervention, epidemics with an infection attack rate of 20-30 % still occur in highly heterogeneous networks, but they become increasingly rare as the variance decreases. As the intervention is directed more towards close contacts, it is more efficient if transmission is predominantly driven by them (figure 3c) than by casual contacts (figure 3e). Using a threshold of 500 cases (5 % of the study population) to define successful containment, the probability of intervention success decreases from 100 to 40 % in the close contact scenario (figure 3c) and from 80 to 20 % in the casual contact scenario (figure 3e) for weakly to highly dispersed degree distributions, respectively.

Moderately contagious influenza strains

For moderately contagious influenza strains, the size of the epidemic depends on heterogeneity in the degree distribution even when no interventions are performed (figure 3b). The average number of infections increases from $\sim$1000 when the variance is low to $\sim$3000 when the variance is high. The variability in the size of the epidemics is inversely related to the dispersion in the degree distribution, as indicated by the coefficient of variation which decreases from 100 % for epidemics resulting from weakly heterogeneous degree distributions to 40 % for epidemics resulting from highly heterogeneous degree distributions. The increasing size and the decreasing variability of the epidemics make the distinction between small outbreaks and vast epidemics more pronounced as the variance increases. The probability of an epidemic increases from 50 to 85 % for weakly to highly heterogeneous degree distributions. For moderately contagious influenza strains, the intervention efficiently controls epidemics in networks with low variance (figure 3d, f). For networks with higher variance, however, the probability of successful containment decreases to 80 % (figure 3d) and to 50 % (figure 3f), depending on whether the infection is predominantly transmitted to close or casual contacts.
Figure 2: Examples of simulated epidemics in populations with different network structures. Each graph gives three realizations resulting from the degree distribution shown in the inset. The degree distribution is fixed for the three realizations, respectively, but epidemiological factors (e.g. the time of infection of high-degree individuals or the duration of their infectious period) are subject to random variation given the parameters listed in table 1. Infection attack rates (IARs) of the epidemics are shown in the legend. The six epidemics are a subset of the scenario in figure 3b. (a): Epidemics in a highly heterogeneous network (SD=13.5) with a maximum degree of $D_{\text{max}}=479$ contacts. (b): Epidemics in a network with lower standard deviation (SD=4.2) with $D_{\text{max}}=33$ contacts.
Figure 3: Distributions of the sizes of outbreaks and epidemics occurring under different networks and transmission modes. Left column: Highly contagious influenza strain causing an infection attack rate of \(\sim 50\%\). Right column: Moderately contagious influenza strain causing an infection attack rate of up to \(\sim 30\%\). Epidemic outcomes under no intervention (a,b). Effects of intervention are shown dependent on whether infection is predominantly transmitted to close (c,d) or casual (e,f) contacts. Bars have a width of 100 cases. For each graph, 4500 simulations were performed.
2.4. Discussion

Investigating characteristics of a hypothetical influenza epidemic and the effects of intervention under different networks shows that the infection attack rate of an epidemic and the effectiveness of intervention can depend on dispersion in the degree distribution of the number of contacts and the distribution of transmission rates between close and casual contacts. With parameters specifically adjusted to influenza and targeted distribution of antivirals, we have followed a parameter-rich and realistic modelling approach, using networks which are produced by a modified preferential attachment step as a possible representation of contact structures in the population.

Degree distributions with high variance or the occurrence of high-degree individuals can be associated with an accelerated course of the epidemic\(^{83}\) (see also figure 2) and with an increased infection attack rate (figure 3b). The effect on the increased infection attack rate is limited if the infectious agent is highly contagious, i.e. if infection is efficiently transmitted from the outset, producing a self-exhausting infection process that cannot be further propagated by contact patterns (figure 3a). We conclude that heterogeneous degree distributions increase the infection attack rate of epidemics which are produced by moderately effective transmission - and that is the situation when intervention is applied (figures 3c-f). Contact patterns will influence intervention success less, if intervention is targeted geographically\(^{6,38}\), rather than socially, as assumed in this investigation.

Apart from measures of dispersion and clustering in the degree distribution, additional network characteristics influence the epidemiological outcome of an epidemic\(^{13,20}\). The type of network\(^{15,77}\) and the population size\(^{79}\) have an effect on the probability of an epidemic occurring and/or the final size of the epidemic. For the networks studied here in the case of an influenza epidemic, we have found that clustering is a negligible factor with respect to epidemiological outcomes (results not shown). However other studies have shown that clustering can influence the size of the epidemic\(^{94}\), indicating that epidemiological outcomes can be highly network-specific. For a more generalized approach describing the effects of close and casual contact patterns on the epidemics, see\(^{91}\).

The maximum degree in our networks largely determines the variance of the degree distribution and the relationship for the networks used in this investigation is \(\text{Var} = 10.5 + 0.33 D_{\text{max}}\) with \(r^2=0.93\). Thus, epidemiological outcomes may be explained largely by the influence of only one individual in the network, the individual with the highest degree. To date it is not clear to what extent this effect is restricted to networks which are built on the basis of preferential attachment. Extending the present conclusions to a wider class of networks would be an important advance for infectious disease studies.
Lymphatic filariasis and onchocerciasis are subject to major intervention programs of the WHO. The *Onchocerciasis Control Programme* in West Africa has been launched thirty years ago and has led to considerable insights into the control of this infection. The *Global Alliance to Eliminate Lymphatic Filariasis* is a relatively recent control program with ambitious targets concerning its efficacy and its schedule. These expectations are based on certain assumptions about the density-dependent processes of limitation and facilitation which determine eradicability: the levels of transmission thresholds and breakpoints. We review these processes operating in filarial infections and show their impact on the persistence of the parasite, as well as those issues where sound predictions about the eradicability of these infections require better knowledge to develop.

Among the parasitic diseases that result from an infection with filarial nematodes, onchocerciasis and lymphatic filariasis are the two most prevalent diseases, with about 17 million and 120 million people being infected, respectively. As both diseases can substantially impair the individual (pathology, increased mortality) as well as the population (socio-economic development), they are subject to major intervention programs of the WHO. The *Onchocerciasis Control Programme* (OCP), initiated in 1974 in seven West African countries and performed over an extended area until the end of 2002, was based on vector control by aerial application of larvicides. Its successor program, the African Programme for Onchocerciasis Control (APOC), relies mainly on mass drug administration of the microfilaricide ivermectin. The Global Programme to Eliminate Lymphatic Filariasis (GPELF) was launched in 1998 and is based on mass drug administration of various microfilaricides. A fund of practical experiences in the attempt to eliminate a filarial disease is available from the control of onchocerciasis, but questions remain. The OCP achieved elimination in several West African foci, but large-scale elimination seems hardly possible. Recently observed cases of recrudescence give cause for concern that the capacity of the parasite to reinvade its host or the frequency of reintroductions is higher than assumed. This might result from underestimating the effects of mechanisms which stabilize the parasite's persistence in the host population. Besides heterogeneities (e.g. heterogeneity in exposure), regulatory processes in the host-parasite relationship are a main determinant of the persistence (and consequently, of the eradicability) of a parasite. Figure 1 shows density-dependent processes at three stages in the filarial life cycle. These processes are illustrated specifically for onchocerciasis, because the regulatory processes in the human host could be investigated due to the accessibility of the adult worm burden, which can hardly be investigated in lymphatic filariasis.
Figure 1: Density-dependent processes in filarial infections. Parasite life cycle of a filarial infection in the example of *Onchocerca volvulus* and three stages where density-dependent processes have been suggested. (a) Limitation (due to protective immunity against L3) in the establishment of adult parasites is suggested by the observation that in hyperendemic transmission the establishment rate of adult parasites is not proportional to, but rather independent of the ATP. The saturating relationship becomes sigmoid, if facilitation (due to parasite-induced immunosuppression) in the establishment of adult parasites is assumed. (A non-regulated relationship is not represented in (a) because a parasite life cycle must include at least one limitation process to guarantee for a stable equilibrium; throughout, this 'default' process is assumed to be represented by limitation with respect to the ATP. Both curves in (a) result from the equilibrium solution of Eqn 1 in Box 2 with respect to \( w \), the burden of adult female O.v., i.e. \( dw/dt = 0 \).) (b): Limitation in the microfilarial density can result from either a reduction of the life expectancy of Mf (as a consequence of protective immunity) or from density-dependent Mf production (crowding effects which reduce the fecundity of adult female parasites). (c): Both types of density dependence and non-regulation have been demonstrated in vectors and strongly depend on whether or not the vectors (i) have a cibarial armature and/or (ii) form a peritrophic membrane (for an overview in lymphatic filariasis see Ref.\(^{110}\), in onchocerciasis see Ref.\(^{111}\)). Limitation prevails in most vectors, i.e. the probability of successful development into an L3 decreases if many Mf are ingested during the bloodmeal.
The eradicability of lymphatic filariasis was suggested more than 10 years ago\textsuperscript{112}, but it is multi-faceted because intervention programs in some places have achieved elimination very easily, whereas others have not been successful, despite long-term operation\textsuperscript{110,113}. The first well-documented elimination of lymphatic filariasis occurred on Melanesian islands where \textit{Anopheles}-transmitted \textit{Wuchereria bancrofti} infection disappeared accidentally as a side effect of a malaria control campaign based on DDT house spraying\textsuperscript{114}. A second example was reported from villages of a Chinese province where mass drug administration of diethylcarbamazine (DEC) eliminated \textit{Anopheles}-transmitted \textit{Brugia malayi} infection\textsuperscript{115}. Both examples contrast with experiences in those Melanesian islands, where \textit{Aedes}-transmitted \textit{W. bancrofti} infection could not be eliminated despite 50 years of DEC distribution\textsuperscript{110}.

Apparently, control success of lymphatic filariasis is tightly associated with the local parasite/vector combination. As long as 30 years ago, it was suggested that density-dependent processes can differ profoundly between vectors and that this may be the reason for such inconsistent patterns in the success of control programs\textsuperscript{116}. Density-dependent processes can be divided into facilitation and limitation processes (Box 1), regardless of whether they operate in the vector or in the host. Their effects can most appropriately be explained with respect to eradicability, because facilitation processes will 'facilitate' the eradicability of a parasite, whereas limitation processes will 'limit' the prospects of such a success. The interaction between both types of density dependence determines the existence and levels of breakpoints and transmission thresholds, which are defined as follows:

\textbf{Transmission thresholds} refer to a vector density below which the infection cannot persist. If there are too few vectors, an adult parasite will die before any of its offspring is transmitted and consequently, the infection does not get transmitted. The validity of this concept, which applies for all vector-borne infections, was already demonstrated by Ross, who investigated the transmission dynamics of malaria\textsuperscript{1}. A key variable is the rate at which vectors feed on human hosts per unit of time, the annual biting rate (ABR). The threshold below which the infection cannot persist, the threshold biting rate (TBR), is a measure for the persistence of the parasite population\textsuperscript{117}. The values of the TBR vary considerably between parasite subspecies (for examples see Refs.\textsuperscript{118-121}) and depend on the density-dependent processes operating in vectors and hosts and on the heterogeneity in contact rates between vectors and hosts.

\textbf{Breakpoints} refer to a parasite density below which the infection cannot persist. The reasons for the existence of breakpoints are best explained by the mating process, first described mathematically for schistosomiasis\textsuperscript{122}: as transmission depends on sexual reproduction of the parasite, an individual must harbour at least one female and one male parasite to contribute to the transmission of the infection. Averaged over the population, however, breakpoints do not necessarily lie at two parasites per host, but may even be relevant for control measures if falling short of one parasite per host. The mating process transforms the process of microfilariae production by adult female worms into a facilitation process because mating (and hence reproduction) becomes increasingly facilitated at high parasite burdens. Breakpoints in the transmission of filarial infections have been only rudimentarily investigated, but sug-
gested to be relevant for the elimination of lymphatic filariasis (see paragraph Density-dependent processes in vectors).

Thresholds and breakpoints form the important points in a persistence graph which is explained in Figure 2. Such a graph shows how equilibrium parasite burdens, transmission thresholds and breakpoints depend on the number of vector-host contacts and thereby allows the eradicability of an infection to be assessed. The persistence graph is derived from ABR-specific equilibrium solutions of mathematical models of which a basic one, used in the present manuscript, is described in Box 2.

**Figure 2**: Persistence curve for filarial infections. The persistence curves show equilibrium parasite densities dependent on the number of vector-host contacts (ABR). The **red curve** shows the stable, positive equilibria: provided that there are sufficient vector-host contacts and parasites, the average parasite density in human hosts is represented by this curve. The **green line** shows the stable, trivial equilibria (parasite density=0): transmission of the infection is not possible because of too few vector-host contacts or too few parasites. The **blue-dotted curve**, resulting from breakpoint-inducing facilitation processes, represents the unstable equilibria (breakpoints): if the parasite density falls short of a breakpoint, the system will tend towards the trivial equilibrium and the infection will go extinct without further efforts (successful intervention, C1). If the parasite density exceeds a breakpoint, the system will return to the stable, positive equilibrium and the infection will continue to persist (untimely cancelled intervention, C2). Vertical **arrows** represents the dynamical behaviour of the system: starting from any point on a line, an arrow points to the equilibrium parasite density at which the undisturbed system will stabilize. In the **green part** of the graph, the infection cannot persist because the critical transmission threshold (threshold biting rate (TBR), point A) is not reached. In the **blue part**, the infection can be eliminated by reducing the parasite density below the ABR-specific breakpoint. Point B indicates an ABR at which facilitation-induced breakpoints disappear so that the stable zero-equilibria (green line) exist only because of the mating process. Breakpoints can be so close to the zero-equilibrium that they are not relevant for elimination (represented by the smooth transition from the blue into the red part of the graph).
3.1. Density-dependent processes in vectors

Before going into details of facilitation and limitation, it will be helpful to consider the case of non-regulated transmission by vectors. In this case, a constant percentage of microfilariae (Mf) ingested by the vector during a bloodmeal develops to the infective stage and hence, the number of infectious larvae (L3) per fly increases linearly with the Mf density in the skin of infected hosts. Limitation and facilitation in vectors cause deviations from this linear relationship as shown in Figure 1c.

Limitation is associated with the fact that no population (e.g. the number of parasites per fly) can increase indefinitely. In vectors, this means that the relationship between Mf intake and L3-output is only initially linear and approaches a constant value with increasing Mf intake. This relationship can be found in vectors of both, lymphatic filariasis and onchocerciasis \(^{111,116,123,124}\). In the simplest case, limitation in vectors results from an excess mortality, caused by too many Mf ingested. If the survival of vectors is profoundly affected, it may even be possible that the average number of L3 per fly decreases at high Mf densities \(^{118}\). Compared to the non-regulated (linear) case, transmission in the case of limitation can be more efficient at low Mf densities and maximum transmission is guaranteed over a wide range of high Mf densities (this occurs due to the fact that both relationships must intersect to explain an identical equilibrium, implying that the limited process is 'over-efficient' before, and 'under-efficient' after this intersection).

Limitation processes counteract the eradicability of an infection by shifting transmission thresholds towards lower values which require higher control efforts to be achieved.

Facilitation has been observed in anopheline mosquitoes \(^{116,124,125}\) and in Simulium species transmitting Amazonian onchocerciasis \(^{111}\). These vectors possess a cibarial armature, a tooth-like chitin structure which lacerates ingested Mf. At low Mf densities, this cibarial armature substantially reduces the proportion of surviving Mf and, as a result, transmission is inefficient and transmission thresholds are shifted towards higher values, which can more easily be achieved by control measures. At high Mf densities, however, the cibarial armature may be inefficient because it is masked by a few Mf promoting the survival of the others (The observation of this process had led to the introduction of the term facilitation). Since limitation must occur at higher Mf densities, the facilitation curve in Figure 1c becomes sigmoid (for simplicity, the term 'facilitation' is used in the following as a short form for 'initial facilitation with associated limitation').

The eradicability of filarial infections which are subject to facilitation processes does profit not only from threshold shifts, but also from the fact that facilitation leads to unstable transmission \(^{116,126}\), synonymous with the existence of breakpoints (Box 1). Although the mathematical approach and to some extent also the data investigation involved in this approach have been criticized \(^{127}\), it seems to be a rule that facilitation processes shift the persistence graph to the right, i.e. they increase transmission thresholds and induce breakpoints into the transmission of an infection. The question then remains as to whether or not a certain facilitation process is practically relevant for an intervention program \(^{125,128,129}\). Detailed information about the degree of limitation and facilitation, remains an absolute requirement for the precise determination of the location of breakpoints.
3.2. Density-dependent processes in the human host

The processes in the vectors are not the only factors that determine the eradicability of a filarial infection; the processes that operate in the human host are also important. In onchocerciasis, these can more easily be investigated due to the availability of nodulectomy data. Unlike adult parasites in lymphatic filariasis, which are difficult to localise and cannot be removed from the host tissue, adult *Onchocerca volvulus* aggregate in subdermal nodules (onchocercomata), some of which can be palpated and surgically excised, providing quantitative measures for the parasite population, the endemicity and intensity of infection. Although only a fraction of parasites is accessible by nodulectomy, the true parasite burden can be estimated and used to investigate feedback mechanisms, which can operate in many stages of the intra-host life cycle of the parasite.

The first immunological mystery occurs as early as the stage of parasite acquisition: of several thousands of infectious larvae (L3) to which a human host is annually exposed (annual transmission potential, ATP), only a few manage to develop into an adult parasite. Surprisingly, the number of successfully maturing L3 seems to be almost constant in hyperendemic transmission, i.e. high ATPs do not mean high numbers of maturing L3s necessarily. This is confirmed by infection experiments in jirds, which have shown that only at low doses does a proportionality occur between the dose of infection and the number of established parasites; higher infection doses do not increase considerably the number of successfully establishing L3s. Although studies in the *Brugia* mouse model have provided further insights into the immunological role of L3s, little is known as to how the sum of the various immunological processes will influence intervention campaigns. We still do not understand by which mechanism a human body is protected against infection by the presence of thousands of L3, but the responsible process certainly is highly limited with respect to the ATP and thus compromises efforts to eliminate the parasite.

Parasite acquisition does not only depend on the vector-related force of infection, but has also been suggested to depend on the parasite density in the human host. Density-dependent parasite establishment could be a consequence of parasite-induced immunosuppression, which seems to be a mechanism involved in most filarial infections and might even be involved in most nematode infections. Immunosuppression is assumed not only to promote parasite persistence within the host, but also to increase the susceptibility of the host to superinfection. This is a facilitation process in that parasites that have already established themselves in the host increase the rate at which further parasites are acquired. This means that an already established parasite reduces the period of time until an infection with the next parasite can occur (a process which necessarily needs to be associated with a limitation process). Facilitated infection rates introduce breakpoints into the transmission of an infection, also known from ecology as the Allee-effect. As in the example of facilitation in the vectors, this process helps to eradicate the infection: during a control campaign, the reducing parasite density results in an increasing immunological competence of hosts which, in turn, helps reducing the parasite burden. A consequence of this positive feedback is that the infection will cease if it goes under a certain parasite density. If two or more facilitation processes are
combined, transmission thresholds and breakpoints can be shifted towards values that are highly relevant for intervention programs.

Benefits resulting from facilitation processes may be balanced or even overridden by coexisting limitation processes. In onchocerciasis, the investigation of nodulectomy data clarified the relationship between the burden of adult parasites and the microfilarial density in the skin\textsuperscript{108}. Whereas the Mf density increases almost proportionally with the burden of adult \textit{O. volvulus} of the forest strain (linear relationship), the relationship in savannah onchocerciasis is non-linear, showing considerable limitation. From this point of view, elimination of savannah onchocerciasis is more difficult to achieve than that of forest onchocerciasis. Figure 3 illustrates the effects described by summarizing how limitation and facilitation processes in vectors and human hosts modify the eradicability of a filarial infection. To provide analyses based on parameter values estimated from data, the effects are illustrated in the example of onchocerciasis.

**Figure 3**: Density-dependent processes modifying eradicability. Persistence graphs which result from density-dependent processes operating at different stages of the parasitic life cycle. The pale-coloured curve in each graph represents the persistence pattern that results if there is no density dependence (all processes are non-regulated except the limited relationship between parasite establishment and ATP, Eqn 3 in Box 2). The threshold biting rate (TBR) lies at \(~850\) bites per person per year (bpy), and breakpoints result only from the mating process. Parameter values refer to West African savannah onchocerciasis as outlined in Box 2. \textbf{Adult} : Number of adult female parasites establishing per year in a host (Eqn 3 in Box 2). \textbf{Mf} : Microfilarial density in the skin dependent on the number of adult female parasites in the human host (Eqn 4 in Box 2). \textbf{L3} : Number of L3 developing in a fly from Mf ingested during preceding bloodmeals (Eqn 5 in Box 2). \textbf{(a)}: Persistence graph resulting from facilitated parasite establishment: the transmission threshold increases to a TBR of \(~2200\) bpy, and breakpoints are shifted considerably towards higher parasite burdens, indicating facilitated eradicability. \textbf{(b)}: Limitation in the Mf density complicates control measures because the transmission threshold decreases to a TBR of \(~700\) bpy and, accordingly, the breakpoints are shifted towards lower parasite burdens. \textbf{(c)}: Limitation in flies also worsens the prospects of elimination by decreasing the transmission threshold to a TBR of \(~900\) bpy. \textbf{(d)} shows the persistence graph under the assumption that the density-dependent processes in a, b and c operate simultaneously. In this example, the parameter values chosen for the three processes yield a TBR which is still more pessimistic compared to the case of non-regulation in all three processes, i.e. the effects of the two limitation processes outbalance the facilitation process.
3.3. Sources of uncertainty

Apart from differences in the persistence patterns between the specific parasite-vector-host combinations, there are sources of uncertainty which similarly affect all subtypes of these infections. This can be shown by two sensitivity analyses, one referring to a parameter in the transmission cycle and the other referring to interventions by microfilaricides.

One of the least known processes in the transmission cycle of filarial infections is the relationship between the ATP and the parasite establishment rate (PER, i.e. the number of adult parasites actually establishing in a host per year). Whereas the ATP usually ranges from some dozens up to several thousands of L3 per host per year, the PER usually amounts to a few parasites per host per year, in onchocerciasis hardly exceeding values over five per year even at high ATPs. Limited parasite establishment, which has also been investigated with respect to the microfilarial density, is in the present model linked to the ATP by parameter $\alpha$ (Eqn 3 in Box 2). Other models usually implement this functionality by the immunological competence of hosts which, in turn, helps to control the microfilaremia in the course of therapy. The microfilaricidal effect mimics a reduction in the reproductive capacity of adult female parasites and shifts the persistence graph to the right. (In contrast, vector control is not a 'persistence-shifting' intervention because it does not primarily alter the regulatory processes within parasites, vectors or hosts). Dependent on slightly different assumptions in the density-dependent efficacy of the microfilaricide, the three scenarios shown in Figure 4 produce transmission thresholds of 25,000, 15,000 and 10,000 bites per person per year, and the location of breakpoints can differ by orders of magnitude, if compared at identical ABRs. This shows that the decisive factor in the eradicability of a filarial infection with a microfilaricide is not its efficacy in the heavily infected population (in the beginning of control), but its efficacy in the almost 'cured' population (with low Mf densities after a certain time of control). Predictions of the long-term effects of an intervention based on microfilaricides seem impossible without first having clarified the density-dependent effects associated with their administration.
Variations in the density-dependent processes between vectors, parasites and hosts can lead to profoundly different persistence patterns (see above). The eradicability of a filarial infection will depend on the opposing processes of facilitation and limitation. Predictions of the success of intervention programs will be over-optimistic if the degree of facilitation is underestimated or if the degree of limitation is overestimated and over-pessimistic if the degree of facilitation is underestimated or if the degree of limitation is overestimated. Sensitivity analyses have established that, for example, the relationship between the ATP and the establishment of adult parasites or density-dependent side effects of microfilaricides are sources of uncertainty that can seriously affect the eradicability of an infection.

Figure 4: Persistence-shifting intervention and uncertainties. The eradicability of a filarial infection can also be affected by density-dependent side effects of certain interventions (see paragraph ‘Sources of uncertainty’). The figure shows how the persistence graph (upper graphs, colours as in Figure 1) is altered by administration of a microfilaricide. The pale-coloured curve in each graph represents the persistence pattern without intervention (density-dependent processes as in Figure 3d). The full-coloured curves represent the persistence patterns resulting from a microfilaricide-based intervention, whereby density-dependent characteristics of the microfilaricidal effect are shown in the lower graphs. In the three scenarios, the microfilaricide reduces the Mf density by 95% on the population level, but can density-dependently deviate from this by 2%. (a) refers to an effect which might result from ivermectin-facilitated immunity. As a result of this mechanism, the reduction in the Mf density improves in (a) from 95% to 97% during the course of therapy (from right to left in the upper graph). The corresponding persistence graph shows that under this assumption the TBR increases from ~900 to ~25,000 bites per person per year, suggesting that elimination might be easily achieved. Compared to the TBR of ~15,000 in the case of no density dependence (scenario (b), 95% reduction independent of the Mf density), a mechanism like ivermectin-facilitated immunity can considerably increase the prospects of elimination. In scenario (c) -chosen with respect to symmetry to (a)- the reduction in the Mf density declines from 95% to 93% during the course of therapy (from right to left in the upper graph), which shifts the TBR to ~11,000 bites per person per year. The examples show that a slight variation of density-dependent side effects of an intervention can considerably alter the prospects of elimination.

3.4. Eradicability and predictability
Mathematical models and computer simulations have been employed in planning control strategies and evaluating intervention success of onchocerciasis and lymphatic filariasis, and criticism about their applicability and their predictive capacity has been raised. As such models will always translate our input (e.g. regulatory processes) into some output (e.g. a prediction of intervention success at a certain time), their predictive capacity directly reflects our level of knowledge. If our knowledge is poor, a mathematical model will poorly reproduce reality - actually a useful implication because it can verify if our knowledge about the infection is sufficiently complete. It is impossible to build mathematical models that, at the same time, maximize realism, generality and precision. The model presented here is developed for the purpose of generality, allowing a comparative analysis which intends to maximize the understanding how the processes impact on the eradicability of a filarial infection. Models which maximize realism and precision must consider, for example, demographic and stochastic aspects, the age-structure of the population, heterogeneities among parasites and hosts and the epidemiological significance of zoophily of vectors and animal reservoirs.

Although logistic successes (availability of microfilaricides and broad participation of countries) in the beginning of GPELF have been noted, it is not yet clear if mass drug administration of microfilaricides can efficiently perturb the stabilizing processes within the host-parasite relationship. The patchy distribution of different vector-parasite combinations makes it difficult to talk about the eradicability of lymphatic filariasis as a whole. Instead, we should refer to the elimination of the infection in its specific context of parasite strain, vector and density-dependent processes operating in both, vectors and hosts. Precise predictions of the prospects of success of the GPELF would profit from improving methods like ultrasound techniques that allow for the quantification of the adult parasite burden to investigate the regulatory processes in the human host.

The experiences made during the OCP have shown that certain risk factors can challenge the large-scale and long-term success of interventions. For example, infections that are imported by flies migrating from endemic into controlled regions will be overly compromising if we ignore important limitation processes which increase the capacity of the parasite to re-invade the population and persist at low transmission intensities. On the other hand, if we neglect important facilitation processes, which promote eradicability, then we will miss chances in those stages of an intervention campaign when the elimination of the parasite is within reach. The latter may be especially relevant for the Onchocerciasis Elimination Programme of the Americas (OEPA) which has yielded promising results. Density-dependent processes determine eradicability - their identification should be an integral part in our strategies to eliminate or eradicate a parasite.
### 3.5. Box 1: Glossary of terms

<table>
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<tr>
<th>Term</th>
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<tr>
<td><strong>ABR</strong></td>
<td>Annual biting rate (number of vectors that take a bloodmeal on one human host per year).</td>
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<tr>
<td><strong>ATP</strong></td>
<td>Annual transmission potential (average number of infective larvae (L3) transmitted to one human host per year).</td>
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<td><strong>Breakpoint</strong></td>
<td>A parasite number or density below which infection cannot persist. Breakpoints can be determined for each parasite stage and also for the ATP; they represent ABR-specific, unstable equilibria, resulting from facilitation processes.</td>
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<tr>
<td><strong>Control</strong></td>
<td>Reduction of the incidence of infection to a certain level where the disease is considered to be no longer a public health problem(^{98,99}).</td>
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<tr>
<td><strong>Density-dependent processes</strong></td>
<td>Regulatory processes in the vector-parasite-host relationship which depend in a nonlinear way on the parasite density, i.e. the number of parasites per host (see also facilitation and limitation).</td>
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<tr>
<td><strong>Elimination</strong></td>
<td>Local reduction to zero of the incidence of infection; since infection can be imported from other areas which are still endemic, permanent intervention is required(^{98,99}) to maintain elimination as a stable state, i.e. the trivial equilibrium.</td>
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<tr>
<td><strong>Equilibrium</strong></td>
<td>A parasite density (here: adult parasites per host, Mf per mg skin snip, L3 per fly or ATP) which is sufficiently constant over a long period of time. The equilibrium solution of a mathematical model results from setting the derivatives equal to zero such that there is no longer a change in the variables. The term 'trivial equilibrium' describes the zero-equilibrium which is stable in the case of facilitation and unstable in the case of limitation. Positive unstable equilibria are synonyms for breakpoints.</td>
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<tr>
<td><strong>Eradication</strong></td>
<td>Global reduction to zero of the incidence of infection; once achieved, further interventions are not necessary(^{98,99}) (Eradicability is a term often used in a broader sense, without discriminating between the local and the global aspect).</td>
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<tr>
<td><strong>Facilitation</strong></td>
<td>A positive feedback process in which a parasite (of any stage) promotes the success of parasites of the same or of another stage, regarding survival, development, reproductivity, etc. As any population is limited in space, reproductivity, etc., a facilitation process must be associated with at least one 'stronger' limitation process. For sufficiently high ABRs, a data-based comparison between a facilitated and a non-regulated relationship implies an intersection between both relationships at an unstable equilibrium (breakpoint) (the stable equilibrium must originate from the associated limitation process which leads to a second intersection). The facilitated relationship falls short of the non-regulated relationship before the breakpoint (it is 'under-efficient'), shifting the transmission threshold towards a higher value. Due to the induction of breakpoints and the 'under-efficacy' at low parasite densities, facilitation processes can positively influence ('facilitate') the eradicability of an infection.</td>
</tr>
<tr>
<td><strong>Limitation</strong></td>
<td>A negative feedback process in which a parasite (of any stage) compromises the success of parasites of the same or of another stage, regarding survival, development, reproductivity, etc. As any population is limited in space, reproductivity, etc., limitation must be the rule. However, it is possible that the limited part of the process is not yet, or may not be observable. For sufficiently high ABRs, a data-based comparison between a limited and a non-regulated relationship implies an intersection between both relationships at the common, stable equilibrium value. The limiting relationship exceeds the non-regulated relationship before the stable equilibrium (it is 'over-efficient'). Due to 'over-efficacy' at low parasite densities, limitation processes decrease transmission thresholds and breakpoints and thereby negatively influence ('limit') the eradicability of an infection.</td>
</tr>
<tr>
<td><strong>Superinfection</strong></td>
<td>In the context of filarial diseases used for describing the process of infection with a new parasite while being already infected with one or more parasites of the same species.</td>
</tr>
<tr>
<td><strong>TBR</strong></td>
<td>Threshold biting rate (an ABR below which the infection cannot persist). A more general term is transmission threshold.</td>
</tr>
<tr>
<td><strong>Transmission threshold</strong></td>
<td>A vector density below which infection cannot persist (see also TBR).</td>
</tr>
</tbody>
</table>
3.6. Box 2: Basic model for the transmission of a filarial infection.

To provide a comprehensible modeling framework, the transmission cycle of a filarial infection is described deterministically, neglecting the age structure of the human population. Parameter values are adapted to West African savannah onchocerciasis for which regulatory processes are better investigated. The changes in the burdens of adult female parasites, \( w \), and microfilariae, \( m \), with time \( t \) are given by

\[
\frac{dw}{dt} = \lambda(w, ATP) - (\sigma_w + \sigma_h)w \quad (1)
\]

\[
\frac{dm}{dt} = \varphi(w)\beta(w) - (\sigma_m + \sigma_h)m \quad (2)
\]

Where \( ATP = \) Annual transmission potential; \( \lambda = \) Parasite establishment rate (PER), \( 1/\sigma_w = 10 \) years: Life-expectancy of adult female parasites\(^{133,148}\); \( 1/\sigma_h = 50 \) years: Life-expectancy of humans, \( \varphi = \) Mating probability, for promiscuous parasites given by \( \varphi(w) = 1 + (k/(k+w))^i - 2^{i-1} (k/(2k+w))^i \)\(^{149,150}\), whereby adult female \( O. volvulus \) are suggested to be geometrically distributed, hence \( k \approx 1^{154} \); \( \beta = \) Rate at which Mf per mg skin snip result from the number of adult female \( O. volvulus \) per year. \( 1/\sigma_m = 1 \) year: Life-expectancy of Mf\(^{133} \). The coexistence of immunosuppression and protective immunity in human hosts is assumed to operate on the PER, implemented as

\[
\lambda(w, ATP) = \lambda_0 f_F(w) f_L(ATP) \quad (3)
\]

Where \( \lambda_0 = 1 \) per year: Number of adult female parasites establishing in a non-infected host per year; \( f_F(w) = (1 + c s w)/(1 + s w) \) : Facilitated parasite establishment due to parasite-induced immunosuppression with parameters \( \lambda_0 c = 5.75 \) per year: Number of adult female parasites establishing in a heavily infected host per year; \( s = 0.1 \): Slope by which \( \lambda_0 c \) is achieved (modified from Ref.\(^{107}\)); \( f_L(ATP) = (\alpha ATP)/(1 + \alpha ATP) \): Limited parasite establishment due to protective immunity against L3 with parameter \( \alpha = 0.06 \) (hypothetical value, chosen to provide a baseline threshold biting rate (TBR) comparable to existing, deterministic onchocerciasis models\(^{118,120}\)). Limitation for Mf is implemented as

\[
\beta(w) = \frac{b w \sigma_w}{1 + k w} \quad (4)
\]

\( b = 5 \) Mf per mg skin snip are contributed per adult female worm in hosts with low parasite burdens; \( k = 0.034 \): slope by which the asymptote \( b \sigma_m \) \( /k = 147 \) Mf per skin snip is achieved (modified from Ref.\(^{108}\)).

Survival of flies -with respect to the time-dependent processes- is assumed to be negligibly small so that it does not need to be implemented dynamically. Limitation in the number of L3 developing from Mf ingested during a bloodmeal is adopted from Ref.\(^{120}\):

\[
l(m) = \frac{a_1 m}{1 + a_2 m} \quad (5)
\]
with \( a_1 = 0.021 \) and \( a_2 = 0.0088 \). According to pre-control OCP data, the ATP increases linearly with the annual biting rate (ABR) at slope \( \varepsilon = 0.02 \), thus

\[
ATP = \varepsilon \text{ ABR} \frac{l}{l^*} \quad (6)
\]

Numerical solutions of the model have been evaluated with initial values of \( w(0) = w_0 \) and \( m(0) = 0.1 w_0 \). If \( w_0 \) leads to the trivial equilibrium of \( w = 0 \), then, either the TBR has not been achieved or a breakpoint has been under-run. If \( w_0 \) leads to an equilibrium of \( w > 0 \), then, an endemic state is possible and a stable equilibrium has been reached. For all combinations of processes, the equilibrium solutions \((t \to \infty)\) for high ABRs are: \( w^* = 40 \) adult female parasites per human host, \( m^* = 75 \) Mf per mg skin snip, \( l^* = 1 \) infectious larva per fly. Parameter values for non-regulated relationships are chosen such that the equilibria are identical to the corresponding regulated relationship.
4. **Stochastic approach: Estimating the rate at which humans are infected with parasites**

Onchocerciasis has been successfully controlled for many years in endemic countries, but more than 120 million people are still at risk. Factors which stabilize the persistence of the parasite in the population must be studied to minimize the future risk of reinfection. Among these factors, the relationship between the annual transmission potential (ATP) and the parasite establishment rate (PER) is a determinant which has to date not been quantified. Using entomological information and palpation data collected by the Onchocerciasis Control Programme in West Africa (OCP) prior to the initiation of control activities, we derive ATP-dependent estimates of the PER from statistical analyses and computer simulations. Even at very low transmission intensities, the filarial parasite *Onchocerca volvulus* can efficiently establish in the human population, originating from an infection process which is strongly limited with respect to the ATP. Implementing the estimates into a simplified transmission model predicts that the critical annual biting rate, below which transmission is not possible, is much lower than previously assumed. We conclude that the risk of reinfection is higher than previously assumed.

4.1. **Introduction**

A main determinant of the eradicability of filarial infections is the relationship between the annual transmission potential (ATP, the annual number of infectious larvae transmitted by vectors to a human host) and the parasite establishment rate (PER, number of adult female parasites successfully establishing in a host per year)\(^1\). In contrast to the ATP, which can roughly be estimated from fly-catching experiments and has been routinely monitored during the Onchocerciasis Control Programme (OCP), the PER is experimentally not accessible and has not been determined to date. Thus, the PER is a major source of uncertainty within the transmission cycle, challenging our efforts to predict either the outcome of interventions or the risk of the infection re-establishing itself in a population. Relationships between the ATP and the PER can be classified into two categories, non-regulated and regulated. In a non-regulated relationship, the PER grows linearly with the ATP, implying that a constant proportion of infectious larvae (L3) successfully develop into the adult stage irrespective of the ATP. The linear relationship yields an optimistic prediction of the outcome of a control program because any effort to decrease the ATP proportionally diminishes the establishment of new parasites. In a regulated relationship of the limitation type, the PER is proportional to the ATP only for low values of ATP. As ATP increases, PER approaches a limiting value. Figure 1 outlines the consequences for a control program: the greater the degree of limitation, the greater the efforts of control must become to achieve a given reduction in the PER. These
considerations apply also to the problem of reinfection in a post-control situation with which the African Programme for Onchocerciasis Control (APOC) may be confronted: the greater the degree of limitation, the greater the likelihood and intensity of reinfection.

The present investigation quantifies the relationship between the PER and the ATP for West African onchocerciasis to support predictions into the prospects of success of future control or the risk of recrudescence. Several investigations relate the prevalence of infection or the microfilarial density to the ATP\[^{118,144,152-154}\]. In such indirect approaches, however, the actual degree of limitation cannot be determined because the prevalence is intrinsically limited to a value of 100% and the production and life-expectancy of microfilariae can involve additional steps of limitation\[^{108,109}\]. Furthermore, it is important to assess the adult worm population directly because it represents the long-living parasite stage within the transmission cycle and therefore is a main determinant of infection persistence.

The manuscript is complemented with Appendices. In Appendix 1 we descriptively present the data to allow for comparisons with the data of earlier publications by showing the relationships among traditional measures like the ATP, the community microfilarial load (CMFL) and the prevalence of skin snip positive people. In Appendix 2, we investigate parasite establishment under the hypothesis of facilitated parasite establishment, i.e. when the PER increases with the host's parasite burden because of immunosuppressive processes induced by already established parasites\[^{107}\]. Estimators for the PER under this hypothesis cannot be given in a mathematically closed form, but must be derived from computer-intensive simulations which furthermore allow for considering additional information and constrictions. Finally, Appendix 3 provides background information on the estimation of the threshold biting rate as derived in a previous modeling approach\[^{151}\].

![Figure 1](image-url)

**Figure 1.** A-C: Control success achievable by a certain control effort starting from a pre-control situation, illustrated by three relationships between the parasite establishment rate (PER) and the annual transmission potential (ATP). All three scenarios assume that the control program reduces the ATP by 90%. The corresponding reductions in the PER are 90% (A, non-regulation), 70% (B, weak limitation) and 20% (C, strong limitation). D: Corresponding effects in the recrudescence during a post-control situation, comparing the relationships in B and C and assuming that the ATP temporarily returns to 10% of the pre-control level. The PER returns to 30% (weak limitation) or to 80% (strong limitation) of its pre-control level.
4.2. Methods

The data were extracted in 2002 from the database of the Onchocerciasis Control Programme (OCP), Ouagadougou. We selected all villages in the OCP area for which a detailed survey with nodule palpation was performed, i.e. 235 villages in 9 countries (Burkina Faso, Benin, Cote d’Ivoire, Ghana, Guinea, Mali, Niger, Sierra Leone, Togo) comprising 77,032 persons. To be included in the present analysis a village had to satisfy the following criteria (number of remaining villages is given in brackets):

1) To guarantee for an equilibrium state of the host-parasite system in which biological relationships are not distorted, the survey had to be performed prior to the initiation of control measures in the area [130]. 2) Entomological data (ATP) as well as palpation data were available [73]. 3) Palpation and skin snip diagnosis and demographic information (age, sex, person has not been absent from the village >1 year) existed for at least 70% of the inhabitants [38]. 4) To guarantee for representative estimates obtained from averaging longitudinally fluctuating ATPs (see online supporting material, Figure S1), at least five pre-control ATPs from different years needed to be available for calculating a geometric mean ATP [14], which is insensitive to outliers. Renz has provided detailed investigations into the variability of ATPs [155-157].

Summary information on these 14 villages is provided in Table 1; entomological information and OCP statistics on prevalence and CMFL (community microfilarial load) are presented in Appendix 1. The present analysis depends on pre-control data which were collected between 1975 and 1989. In the early stages of the OCP, vector and parasite characteristics were not part of the monitoring and thus, the contribution of larvae of animal hosts to the ATP in these data is unknown.

Table 1 (see next page): Summary data of villages. The information in all columns (except the last, PER which is estimated) has been extracted in 2002 from the OCP data base in Ouagadougou. Village code: village abbreviations as used in this paper. In the following two columns, OCP numbers of countries, villages and catch points are given in parentheses and geographic coordinates of villages and catch points are provided in brackets in decimal degrees [North-South / East-West]. Persons (total / investigated): Number of inhabitants of a village / number of those included in this study. Survey date: month/year when survey was conducted. Start of vector control: month/year when OCP activities were initiated. Distances between villages and catch points have a precision of about 2 kilometers. No. of ATPs: number of annual transmission potentials recorded in different years prior to control (see also Figure S1). ATP: geometric mean of the ATP values (arithmetic mean of the values transformed by \( \log_{10}(ATP+1) \)) and 95% confidence limits. ABR: geometric mean of the annual biting rates (arithmetic mean of the values transformed by \( \log_{10}(ABR+1) \)) and 95% confidence limits. MF prevalence: percentage of persons testing positive for microfilariae using skin snips. Nodule prevalence: percentage of persons with positive palpation diagnosis. CMFL: Community microfilarial load. PER: parasite establishment rate, as estimated by eq. (2), see Data and Methods.

a Adjusted by the OCP for age and sex according to an OCP standard population [158].

b Not adjusted for age and sex.

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<table>
<thead>
<tr>
<th>Village code</th>
<th>Country</th>
<th>Village (OCP No.)</th>
<th>Persons (total / investigated)</th>
<th>Survey date</th>
<th>Catch Point (OCP No.)</th>
<th>Distance village - catch point [km]</th>
<th>No. of ATPs, ABRs</th>
<th>ATP [95% CI]</th>
<th>ABR [95% CI]</th>
<th>MF prevalence(^a)</th>
<th>Nodule prevalence(^b)</th>
<th>CMFL (^a)</th>
<th>PER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Be398</td>
<td>Benin</td>
<td>WORIA (398)</td>
<td>96 / 75</td>
<td>4/1979</td>
<td>BASSA BARRAGE (2706)</td>
<td>24</td>
<td>10</td>
<td>5</td>
<td>[2; 19]</td>
<td>1,041</td>
<td>70.4</td>
<td>40.0</td>
<td>23.9</td>
</tr>
<tr>
<td>Be399</td>
<td>Benin</td>
<td>MBETEKOUKOU (399)</td>
<td>229 / 185</td>
<td>4/1979</td>
<td>M'BETEKOUKOU (2704)</td>
<td>6</td>
<td>10</td>
<td>574</td>
<td>[337; 981]</td>
<td>51,175</td>
<td>78.0</td>
<td>41.1</td>
<td>19.6</td>
</tr>
<tr>
<td>Be400</td>
<td>Benin</td>
<td>ZOUTO (400)</td>
<td>249 / 201</td>
<td>4/1979</td>
<td>ATCHERIGBE (2709)</td>
<td>1</td>
<td>11</td>
<td>175</td>
<td>[54; 573]</td>
<td>9,056</td>
<td>69.5</td>
<td>30.8</td>
<td>25.8</td>
</tr>
<tr>
<td>Be401</td>
<td>Benin</td>
<td>KOGBETOHOU (401)</td>
<td>136 / 117</td>
<td>2/1987</td>
<td>LANTA (3001)</td>
<td>13</td>
<td>6</td>
<td>11</td>
<td>[2; 64]</td>
<td>1,276</td>
<td>67.7</td>
<td>28.2</td>
<td>27.4</td>
</tr>
<tr>
<td>Gh340</td>
<td>Ghana</td>
<td>ASUKAW KAW (340)</td>
<td>339 / 277</td>
<td>5/1978</td>
<td>ASUKAW KAW (2505)</td>
<td>34</td>
<td>11</td>
<td>80</td>
<td>[30; 219]</td>
<td>6,492</td>
<td>76.0</td>
<td>39.0</td>
<td>14.3</td>
</tr>
<tr>
<td>Gh377</td>
<td>Ghana</td>
<td>KOTO-NKWANTA (377)</td>
<td>300 / 224</td>
<td>5/1978</td>
<td>DODI PAPASE (2507)</td>
<td>2</td>
<td>11</td>
<td>653</td>
<td>[387; 1106]</td>
<td>21,800</td>
<td>66.8</td>
<td>22.8</td>
<td>16.8</td>
</tr>
<tr>
<td>Gh457</td>
<td>Ghana</td>
<td>MONGONORE (457)</td>
<td>117 / 93</td>
<td>4/1982</td>
<td>MONGONORI (1216)</td>
<td>2</td>
<td>10</td>
<td>13</td>
<td>[4; 47]</td>
<td>804</td>
<td>48.6</td>
<td>12.9</td>
<td>13.7</td>
</tr>
<tr>
<td>Gu863</td>
<td>Guinea</td>
<td>DIAMARADOU (863)</td>
<td>71 / 58</td>
<td>4/1986</td>
<td>DIAMARADOU (4304)</td>
<td>0</td>
<td>6</td>
<td>77</td>
<td>[37; 164]</td>
<td>9,194</td>
<td>54.6</td>
<td>13.8</td>
<td>16.7</td>
</tr>
<tr>
<td>Gu867</td>
<td>Guinea</td>
<td>DIAMODOU (867)</td>
<td>187 / 157</td>
<td>4/1986</td>
<td>DIAMODOU (4405)</td>
<td>2</td>
<td>6</td>
<td>31</td>
<td>[7; 146]</td>
<td>6,215</td>
<td>62.1</td>
<td>28.0</td>
<td>10.7</td>
</tr>
<tr>
<td>Gu910</td>
<td>Guinea</td>
<td>FAMOILA (910)</td>
<td>200 / 149</td>
<td>4/1986</td>
<td>GBAHALA (1123)</td>
<td>6</td>
<td>5</td>
<td>10</td>
<td>[1; 88]</td>
<td>1,819</td>
<td>64.9</td>
<td>41.9</td>
<td>21.5</td>
</tr>
<tr>
<td>Ma458</td>
<td>Mali</td>
<td>MANAMBOUGOU (458)</td>
<td>247 / 200</td>
<td>3/1982</td>
<td>TIENFALA (2017)</td>
<td>17</td>
<td>13</td>
<td>191</td>
<td>[114; 322]</td>
<td>13,493</td>
<td>76.5</td>
<td>32.5</td>
<td>54.6</td>
</tr>
<tr>
<td>Ma460</td>
<td>Mali</td>
<td>FOUGADOU (460)</td>
<td>104 / 78</td>
<td>3/1982</td>
<td>TIENFALA (2017)</td>
<td>4</td>
<td>13</td>
<td>191</td>
<td>[114; 322]</td>
<td>13,493</td>
<td>76.9</td>
<td>30.8</td>
<td>69.4</td>
</tr>
<tr>
<td>To14</td>
<td>Togo</td>
<td>DAYES-DODZI (14)</td>
<td>159 / 137</td>
<td>3/1980</td>
<td>DJODJI (2625)</td>
<td>8</td>
<td>11</td>
<td>2,157</td>
<td>[1,462; 3,187]</td>
<td>138,026</td>
<td>78.0</td>
<td>34.3</td>
<td>23.6</td>
</tr>
<tr>
<td>To441</td>
<td>Togo</td>
<td>TOKPO (441)</td>
<td>126 / 103</td>
<td>3/1980</td>
<td>TOKPO (2627)</td>
<td>19</td>
<td>8</td>
<td>119</td>
<td>[78; 183]</td>
<td>7,102</td>
<td>85.1</td>
<td>40.8</td>
<td>44.8</td>
</tr>
</tbody>
</table>

Legend: see page before
Assuming that parasite establishment does not depend on the parasite burden in the host (no within-host facilitation), a crude estimate for the \( PER \) can be derived from the nodule establishment rate, \( NER \). This incidence is given by \( NER_{i} = k_{i} / a_{i} \), whereby \( k_{i} \) denotes the number of nodules palpated in individual \( i \) at age \( a_{i} \). The average, village-specific nodule establishment rate is standardized with respect to age by

\[
NER = \frac{1}{Z} \sum_{i=1}^{n} NER_{i} \frac{z_{a}}{n_{a}}, \quad \text{eq. (1)}
\]

whereby \( Z \) is the total number of persons among all villages, \( n \) is the number of persons in the village under consideration, \( n_{a} \) is the number of persons of age \( a \) in this village and \( z_{a} \) is the number of persons of age \( a \) among all villages. Taking into account that (i) about 30% (\( p=0.3 \)) of nodules can be found by palpation\textsuperscript{133} and that (ii) on average \( m = 2.5 \) adult female worms aggregate in one nodule\textsuperscript{134}, the corresponding incidence of adult female \( O. volvulus \) in a village is

\[
PER = m \frac{NER}{p} = 8.33 NER. \quad \text{eq. (2)}
\]

This is based on the assumption that nodules, once formed, persist because developing female parasites invade already existing nodules rather than forming a new one\textsuperscript{134}. The estimation is based on persons less than 40 years of age such that differential host mortality or degenerative processes of nodules play a negligible role. To make sure that the estimated \( PERs \) are not biased by this truncation, a sensitivity analysis using an age cut-off of 10 years will be performed.

This simple estimation procedure is complemented with a more sophisticated simulation approach, addressing the hypothesis of facilitated parasite establishment and considering factors like the nodule forming process of the parasite, heterogeneous susceptibility of hosts and sensitivity and specificity of palpation diagnosis (Appendix 2).

Linear fits in Figures 2A and S3A result from a simple least squares minimization and are given for purposes of illustration. They do not take into account the uncertainty in the independent variable \( ATP \). Likewise, the error in the dependent variable cannot be adequately considered as the distributions of nodule incidences among the inhabitants of the villages are highly skewed, with most inhabitants having values of zero (children) and few inhabitants showing large values. The mean incidence in a village, therefore, is influenced by the prevalence and by the occurrence of heavily parasitized patients. For these reasons, confidence limits for the fit were not calculated.
4.3. Results

A linear relationship is suggested by plotting the PER against the log-transformed ATP (Figure 2A). The fit is robust against excluding those five villages that are more than 10 km away from the catch point where the ATP was determined (Table 1). Trends deviating from this linear relationship can be noticed for subsets of villages. For instance, in the villages in Guinea (Gu910, Gu867, Gu863), an 8-fold increase in the ATP seems to be associated with a 3-fold decrease in the PER.

The linear relationship on log-ATP already implies considerable limitation in the ATP as shown in Figure 2B. A maximum PER is possible already for ATPs around 500 L3/person/year (Be399) or even below 100 L3/person/year (Gh340). The PER in the village with the highest recorded ATP (To14) does not profoundly differ from a village in the same country, where the ATP is 20 times lower (To441).

![Figure 2](image-url)

**Figure 2.** Relationship between the parasite establishment rate (PER) and the ATP. A: Linear least-squares fit through zero (offset not required, $p=0.34$) on a log-transformed scale: $\text{PER} = 0.14 \log_{10}(\text{ATP}+1)$, with $R^2=0.21$. B: Same data and same fit as in A, but shown on a linear scale to illustrate the degree of limitation.

To make sure that the estimated PERs are not biased by the age cut-off of 40 years estimates were derived also from the subset of patients $\leq 10$ years of age. The estimates of PERs from both subsets are linearly correlated with $r^2=0.72$, confirming that the age cut-off of 40 years does not introduce substantial bias (results not shown).

The estimates of the PERs derived from this simple estimation procedure and those derived from the computer simulations (see Appendix 2) are linearly correlated with $r^2=0.75$, showing that both approaches comparably detect village-specific infection patterns. Under the hypothesis of facilitated parasite establishment, however, the degree of limitation is much more pronounced because of the influence of the antagonizing within-host facilitation process (Figure S3A, B). Fits of the age-dependent nodule burdens are presented in Figure S4 and corresponding estimates are listed in Table S1.
4.4. Discussion

Pre-control data collected prior to activities of the Onchocerciasis Control Programme (OCP) suggest that the parasite *O. volvulus* efficiently establishes in the population even at low transmission intensities in West Africa. We postulate that the rate at which adult female *O. volvulus* establishes shows strong limitation with respect to the ATP, i.e. it rapidly increases at low ATPs and achieves saturation already at moderate ATPs. The biological implication of limitation with respect to the ATP is that the effort of a successful control program must be high and likewise the risk of reinfection in the post-control era is high.

Implementing the PER estimates into a simplified onchocerciasis transmission model\(^{151}\) suggests that the threshold biting rate (TBR, i.e. the annual biting rate below which infection cannot persist) might drop below 100 bites per person per year (see Appendix 3). This is considerably more pessimistic than previous predictions which have estimated TBRs in the order of several hundreds bites per person per year\(^{118,120}\). An underestimation of the degree of limitation may be one of the reasons for over-optimistic model predictions of the eradicability and recrudescence of onchocerciasis\(^{102,159}\).

Model predictions on the eradicability of an infection depend on regulatory processes which determine transmission thresholds and breakpoints\(^{151}\). These processes must be investigated on pre-control data, in which the interactions between parasit es, vectors and hosts are at equilibrium and are not altered by interventions. An intervention shifts the parasite-vector-host system from equilibrium into an artificial state, which no longer allows the investigation of the native system. The data used in the present investigation were collected prior to control, but have limitations as outlined in the Methods section. For example, the intensity of infection was not measured where infection actually took place, but in river-located catching sites which were some distance from the villages with which they were paired. This allowed for efficient tracking of the effects of vector control, but limits the reliability of efforts to quantify the relationship between the ATP and the PER.

**Implications for current control programs**

To protect those populations which are predominantly at risk, control programs focus on regions where the intensity of transmission is high. For investigations into eradicability or recrudescence of the infection, however, the most valuable data originate from regions with a low pre-control level of transmission. In these regions, the host-parasite-vector system is close to the state which is intended to be achieved by control, and this state represents the behaviour of the system at the target line of the control program. If such data are not available, predictions rely on extrapolations of a data-based fit into the state of non-infection (cf. Figure 2 & Figure S3), challenging the reliability of these predictions.

The present results foreshadow problems that the African Programme for Onchocerciasis Control (APOC) may encounter. Mass drug administration of microfilaricides reduces the output of parasites from hosts into the vectors, but the input of parasites from vectors into the host is still possible. If the PER is strongly limited with respect to the
ATP, the microfilaricidal effect may be not strong enough to reduce the ATP to a value which sufficiently protects the host against reinfection. In this case, infection can be reintroduced more quickly and more efficiently than suggested by previous studies\textsuperscript{104,118,144,160,161}.

Such considerations are also relevant for other current control programs based on mass drug administration, for example the Global Programme to Eliminate Lymphatic Filariasis (GPELF)\textsuperscript{97}. The predictability of control success of this program could be particularly enhanced by improving available diagnostics (ultrasound, antigen assays) on adult parasites to allow for investigations into the relationship between the PER and the ATP. Limitation-like relationships between infection rate and infection pressure or between prevalence and infection pressure have been found also for other parasitic diseases, e.g. malaria\textsuperscript{162,163}. Limitation could also account for infection patterns which so far have been explained by other hypotheses, for example vector-independent transmission routes in the case of trypanosomes\textsuperscript{164}.

Immunological consideration

The human host is highly protected against infection with \textit{O. volvulus}, because only a few L3 establish in a host per year despite of many hundreds or thousands of L3 potentially 'offered' by the ATP. Immunological, the pattern of limitation can be interpreted as an initial proportionality between the \textit{PER} and the ATP, followed by a phase in which the \textit{PER} is almost constant, i.e. independent of the ATP. The initial proportionality would imply that protective mechanisms in the human host always eliminate a constant proportion of the L3. Such a "proportionally protective immune response" is not very plausible and to our knowledge there are to date no hypothesis explaining neither this pattern nor the phase of independence between the \textit{PER} and the ATP.

Considerations, involving immunological hypotheses with a 'static' behaviour, may be insufficient to explain the limitation pattern. Alternative explanations could be provided by queuing processes with 'dynamic' properties; for instance that a developing L3 leads to a highly protective, but short-living immune response such that the infection rate depends not on the level of the ATP, but only on the presence of infection. This hypothesis could explain both being protected against the bulk of the infection dose on the one hand and becoming infected in the sense of a rare event on the other hand. It could also explain higher infection rates in infected hosts\textsuperscript{107}, if immunosuppressive influences by the parasite are assumed to shorten the waiting time between successive infections. Although limitation of \textit{PER} appears to involve very simple patterns (proportionality, constancy), finding immunological plausible mechanisms for this effect is apparently more involved.
4.5. Appendix 1: Data, Figure S1, Figure S2

**Figure S1**: Entomological information for the 14 study villages as recorded by the OCP. ATPs are transformed by Log_{10}(ATP+1). **A**: Longitudinal measurements for each village (markers see B). **B**: ATPs by village. Means are indicated by horizontal lines and whiskers denote one standard error of the mean (for numerical information see Table 1). The villages Ma458 and Ma460 have been assigned to the same catch point.

**Figure S2**: Survey statistics determined by the OCP (data see Table 1, village-specific markers see Fig S1B). The community microfilarial load (CMFL) and the prevalence of skin snip-positive persons were adjusted for age and sex according to an OCP standard population. ATP values of different years are village-specifically merged into a geometric mean.
4.6. Appendix 2: Simulation algorithm and estimation procedure for the hypothesis of facilitated parasite establishment

The degree of (extra-host) limitation with respect to the ATP depends on assumptions about intra-host density-dependence which can additionally be involved in the process of parasite establishment. A facilitating intra-host dependence is suggested by the hypothesis that the PER increases with the host's parasite burden, probably caused by immunosuppressive processes induced by already established parasites\textsuperscript{107,141}.

A direct measure for the burden of adult parasites in human onchocerciasis is not available, but we can infer the number of adult female O. volvulus from palpation data in a two step process: 1) Only about 30\% of nodules can be detected by palpation\textsuperscript{133}. Using additional information from skin snip diagnosis, this estimate can be refined as described below. 2) The analysis of nodulectomy data revealed a linear relationship between the number of nodules and the number of adult female O. volvulus located in these nodules\textsuperscript{134}, which allows translating palpation data into the expected parasite burdens. In order to estimate the PER, the establishment of adult worms and the formation and palpation of nodules is simulated and finally fitted to data. A similar algorithm has been used previously\textsuperscript{107} and is extended here by the processes of nodule formation and palpation.

Quantifying the PER under the hypothesis of facilitated parasite establishment cannot be given in a mathematically closed form and thus its estimation relies on computer-intensive simulations as described below. The simulated age-specific distributions of the numbers of palpated nodules are the basis for a quasi maximum likelihood estimation. In accordance with the analysis in the main part of the paper, the PER is estimated from patients $\leq 40$ years of age. Confidence limits for the estimated parameter are determined from the profile likelihood. The validation of the age-specific nodule distributions estimated by these simulations is given in Figure S4 by a comparison with the village-specific palpation data and an empiric moving median calculated from a window with 9 years of age. The validation of the simulation module considering skin snip and palpation diagnosis is provided in a subsequent paper.

**Simulation / estimation algorithm**

The algorithm is derived from a simulation study with nodulectomy data\textsuperscript{107}, and is modified here to estimate parasite establishment from palpation data. In the following, the term 'parasite' is used as a short form for 'adult female O. volvulus'.

The algorithm is structured into the individual-based module B, which yields age-specific distributions of parasite burdens, the village-specific module C, which transforms the distributions simulated in module B into distributions of palpable nodules and finally, the maximum likelihood estimation (module D). These modules are embedded into a minimization routine (module A) which proposes parameter values until the negative log-likelihood converges to its minimum. The simulation can be summarized by the following scheme:
A) Provide proposals for values of parameters to be estimated:

B) Loop, 100,000 individuals. Based on the proposal, draw realizations for

B1) the index of exposure or susceptibility, \( h_i \);
B2) the number of parasites which initially infect individual \( i \)
B3) the number of parasites infecting individual \( i \) in subsequent years

End of B.

C) Village-specific transformations. Based on the proposed parameters,

C1) transform the age-specific parasite distributions into age-specific distributions of nodule numbers,
C2) transform the age-specific nodule distributions into age-specific distributions of nodules which are palpable, and
C3) determine the proportions of true-positive, false-positive and false-negative palpation diagnoses.

End of C

D) Compute the negative log-likelihood based on the simulation results obtained by C2 and C3.

End of A reached when the negative log-likelihood has reached its minimal value: Convergence.

The modules are described in detail below.

In this simulation study, we avoid using distributions with an infinite carrier like the Poisson distribution (PD) or the negative binomial distribution (NBD), which both are commonly used in parasitological analyses. Measures like parasite burdens or infection rates, however, are limited by nature, and simulations which use unlimited distributions will easily exceed such limitations if the number of simulations is high. Therefore, we use the binomial distribution (BiD) instead of the PD, the beta binomial distribution (BBD) instead of the NBD and the beta distribution (BeD) instead of the gamma distribution (cf. heterogeneity, below). The beta distribution - which is also part of the BBD - is either parameterized in its standard form, \( \text{BeD}(\alpha, \beta) \), or by its expectation \( \mu = \frac{\alpha}{\alpha + \beta} \), which yields \( \text{BeD}(\mu, \beta) \) after substituting \( \alpha \) by \( \mu \). With this notation the simulation modules can be specified in detail:

Module A: Minimization

Parameters were estimated using Powell's algorithm, programmed in C++.\(^{165}\) in connection with varying initial values. Estimates together with their 95% confidence limits are provided in Table S1. Confidence limits for the estimated parameters are determined from the profile likelihood\(^{166}\) based on the likelihood ratio with a \( \chi^2 \) asymptotic distribution: the parameter of interest \( \pi \) was minimized (lower CL) or maximized (upper CL) while allowing the vector \( \hat{\nu} \) of the remaining
parameters to vary freely, provided that
\[ 2[\ln L_{\text{opt}} - \ln L(\theta, \hat{\theta})] \leq C \]
whereby \( C = 3.84 \) is the 95% quantile of the \( \chi^2 \) distribution with one degree of freedom. The minimization routine proposes values for the parameter vector \( \hat{\theta} = \lambda_0, s, M, s_p, s_g, \mu_h, \beta_h, \Lambda \) which determines the simulation results as follows:

Module B: Individual-based simulation

B1) Individual heterogeneity: The simulation of an individual’s course of infection starts with sampling a random index of exposure or susceptibility, \( h_i \). This index remains constant throughout the life of the person and accounts for heterogeneity within the population. It is sampled from a BeD(\( \mu_h, \beta_h \)) in the interval \([0,1]\) and is a factor which modifies the establishment rate.

B2) Initial infection: The initial infection of an individual \( i \) occurs at an annual rate of \( \lambda(0) = h_i \lambda_0 \Lambda \), whereby \( \Lambda \) is the maximum number of parasites which can establish in a host per year and \( \lambda_0 \) is the proportion of \( \Lambda \) parasites which establish in the non-infected host. For the choice of the value for \( \Lambda \) see below. The number of parasites that establish in an non-infected host per year is sampled from a BiD(\( \Lambda, h_i \lambda_0 \)). The expected parasite establishment rate in non-infected hosts is then \( \text{PER}_0 = \mu_h \lambda_0 \Lambda \). For each successful parasite, the life span is sampled from a Weibull distribution with survival function \( S(t) = \exp(-0.0001185 t^{3.76}) \), yielding an life expectancy of 10 years \(^{133,148,167} \) with a standard deviation of 3.0 years. The sampling of survival times is identical for superinfection:

B3) Superinfection: We follow the hypothesis of facilitated parasite establishment, represented by the relationship \( \lambda(w_{a+1}) = (\lambda_0 + s w_a)/(1 + s w_a)^{107} \), whereby \( w_a \) denotes the parasite burden of a host of age \( a \), the product \( \lambda(w_{a+1}) \Lambda \) denotes the density-dependent rate at which parasites establish in the host and \( s \) is a measure for the degree of facilitation. The number of establishing parasites \( w \) in individual \( i \) is sampled from a BiD(\( \Lambda, h_i \lambda(w_a) \)). Repeating parts B1-B3 for 100,000 individuals yields age-specific distributions of (True) parasite burdens, \( W_{T,a} \).

Module C: Village-specific transformations of distributions, diagnosis results

C1) Nodule formation: \( W \) adult female \( O. volvulus \) found by nodulectomy aggregate into \( k \) nodules according to a BBD(\( k \mid W-1, \alpha_k, \beta_k \)) with \( \alpha_k = 7.6 \) and \( \beta_k = 11.74^{134} \), and we assume this aggregation process to hold also for the entire parasite population in a human host. Then, the age-specific parasite distributions \( W_{T,a} \) can be transformed into age-specific (True) nodule distributions \( K_{T,a} \) by redistributing \( W_{T,a} \) with the BBD(\( k_P \mid W_T-1, \alpha_K, \beta_K \)).

C2) Palpable nodules: Only a fraction \( \mu_P \) of the nodules is found by palpation\(^{133} \) so that the number of palpable nodules \( k_P \) can be regarded as a sample of the (True) nodule distribution \( K_T \) and thus, follows a BiD(\( k_P \mid K_T, \mu_P \)). As the sensitivity of palpation usually increases with the age of the patient, we allow \( \mu_P \) to increase with age \( a \).
according to $\mu_P(a) = M(s_P \cdot a)/(1 + s_P \cdot a)$. Here, $M$ denotes the maximum proportion of palpable nodules which asymptotically is reached in old patients by slope $s_P$. To allow for variation in the diagnosis by palpation, we take $\mu_P(a)$ as the expectation of a BeD($\mu_P$, $\beta_P$) of which the dispersion parameter $\beta_P$ can age-dependently increase according to $\beta_P(a) = 1 + s_\beta \cdot a$. With the condition $\mu_P(0)$, $\beta_P(0) = 1$ implies a highly skewed distribution at age=0, reflecting that diagnosis in newborns and very young children is not informative. With the condition $s_\beta > 0$, the BeD($\mu_P$, $\beta_P$) can become bell-shaped as age increases and thus allows diagnosis by palpation to become increasingly informative. With these definitions, each age-specific nodule distribution $K_{T,a}$ can be transformed into the corresponding (Palpable) nodule distribution $K_{P,a}$ by redistributing $K_{T,a}$ with the BBD($K_{P,a} \mid K_{T,a}$, $\mu_P(a)$, $\beta_P(a)$).

C3) Diagnosis: $K_{P,a}(0)$ is the relative frequency of patients of age $a$ with negative palpation diagnosis and $K_{T,a}(0)$ is the relative frequency of patients of age $a$ who have no nodules (non-infected). Then, the frequency of patients of age $a$ with a false negative palpation diagnosis is given by $K_{F,a} = K_{P,a}(0) - K_{T,a}(0)$. These frequencies will be related to the observed frequencies of true-positive, false-positive and false-negative palpation diagnoses, whereby diagnosis of microfilariae in skin snips serves as the gold-standard.

**Module D: Maximum Likelihood Estimation and interpretation of parameters**

For each village, the simulation produces age-specific burdens of palpable nodules with parameter vector $\hat{\theta} = \lambda_0, s, M, s_P, s_\beta, \mu_h, \beta_h, \Lambda$, $\hat{\theta}$ is estimated by minimizing the negative log-likelihood, $-\ln L$, given by

$$-\ln L = -\ln \left( \prod_{a=1}^{40} n_{x,a} K_{F,a} \cdot n_{y,a} K_{P,a}(0) \cdot \prod_{z=1}^{w_{z,a}} K_{P,a} \cdot K_{T,a}(0) \right)$$

whereby the indices $x$, $y$ and $z$ refer to false-negative, true-negative and true-positive palpation diagnosis, respectively, $n_{x,a}$ denotes the number of individuals of age $a$ in these groups and $w_{z,a}$ denotes the number of palpated nodules in skin snip positive patients of age $a$.

The parameters can be roughly assigned to the informational content in the data as follows: $\lambda_0$: age of onset of increasing nodule burdens, $s$ : slope by which nodule burdens increase with age, $M$ : proportion of palpable nodules in aged patients, $s_P$ : increase in the proportion of palpable nodules with age, $s_\beta$ : variance in the proportion of palpable nodules, $\mu_h$ : skewness of the distribution of nodule burdens, $\beta_h$ : variance of the nodule distribution. Parameters $M$, $s_P$ and $s_\beta$ mainly control the properties of palpation diagnosis which is presented in a subsequent paper.

**Sensitivity analysis for $\Lambda$**

It is not possible to estimate $\Lambda$ within the algorithm because it is correlated with $\lambda_0$. However, we can derive a guesstimate from the maximum nodule burden observed in the data, given by 22 palpated nodules in a 49 year old
man in the village of Gh377. Taking into account that (i) about 30% of the nodules can be found by palpation\textsuperscript{133} and that (ii) on average 2.5 adult female \textit{O. volvulus} aggregate in one nodule\textsuperscript{134}, these 22 nodules correspond to $22 \times 2.5 / 0.3 \approx 180$ adult female \textit{O. volvulus}. Given the life-expectancy of adult \textit{O. volvulus} with $\approx 10$ years, this man has acquired on average 18 adult female \textit{O. volvulus} per year. Based on this guesstimate and allowing for additional variation, the maximum parasite establishment rate was set to $\Lambda = 50$ parasites per year. Sensitivity analyses based on likelihood ratio tests finally have shown that the fits do not significantly worsen by varying $\Lambda$ in the range of 30-200.

\section*{Results}

Under the hypothesis of facilitated parasite establishment, the degree of limitation is much stronger compared to case of non-facilitation. The \( \text{PER}_0 \) appears almost constant for \( \text{ATP} \geq 50 \) L3/person/year and the factor of proportionality becomes visible only when the \( \text{ATP} \) is represented on a logarithmic scale (Figure S3A). The dependence on the \( \text{ATP} \) is mainly caused by the theoretical point of non-infection (\( \text{ATP}=0 \) implies \( \text{PER}_0=0 \)). Relationships between village-specific \( \text{PER}_0 \)'s are comparable to the findings for the \( \text{PER} \) described in the main part. The correlation between both estimates yields a coefficient of correlation of \( r^2=0.75 \), implying that both approaches comparably detect village-specific differences.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure_s3.png}
\caption{Relationship between the \( \text{ATP} \) and the parasite establishment rate under the hypothesis of intra-host facilitation, represented by \( \text{PER}_0 \) (number of adult female \textit{O. volvulus} annually establishing in a non-infected host). A: Non-linear least-squares fit through zero on a log-transformed scale: \( \text{PER}_0 = 2.9 \log_{10}(\text{ATP}+1)/(1+6.7 \log_{10}(\text{ATP}+1)) \). B: Same data and same fit as in A, but shown on a linear scale to illustrate the degree of limitation. The degree of limitation is much stronger compared to the result for non-regulation within the host, cf. Figure 2.}
\end{figure}

The fits in Figure S4 suggest that the hypothesis of facilitated parasite establishment can adequately describe the process of parasite establishment within the human host. Corresponding estimates are listed in Table S1. Although the model adequately fits the mean, it does not perfectly generate
the skewness of the age-specific nodule distributions, yielding a simulated median which frequently underestimates the empiric median, i.e. the simulated nodule distributions tend to be overly left-skewed.
Figure S4: Nodule burdens of the inhabitants of 14 OCP villages, determined by palpation prior to control. Individual nodule burdens are represented by circles whereby the number of persons harbouring the same nodule burden at the same age is proportional to the area of a circle. The grey line represents the moving median, derived from 9 successive age classes of one year length. The black lines represent the quantiles (97.5, 75, 50 (median, bold) and 25%) of the simulated distribution of nodules (quantiles are not plotted if identical with zero). Abbreviations of village names: see Table 1. Villages are arranged in ascending order of the ATP (geometric means).
Table S1: Estimates obtained by the simulation. 95% confidence limits are given in paranthesis. \(\diamond\): The proportion of palpable nodules is independent of age and equals the value of \(M\). \(\dagger\): The variance of the beta distributed expectation tends to zero and thus the beta binomial distribution approximates the binomial distribution. \(\ddagger\): The variance of the beta distribution tends to zero and thus, the fit of the data requires not the assumption of heterogeneity within the population.
4.7. Appendix 3: Predicting the threshold biting rate

The eradicability of filarial infections can be quantified by transmission thresholds and breakpoints which strongly depend on density-dependent processes operating within the vector-host-parasite system\textsuperscript{151}. We have suggested that the relationship between the parasite establishment rate (\textit{PER}) and the annual transmission potential (\textit{ATP}) is a major source of uncertainty. In the following, we use the previously applied transmission model (see Box 1 in Duerr et al., 2005) to refine the estimates for the threshold biting rate (\textit{TBR}), which is the annual biting rate (\textit{ABR}) below which the parasite cannot persist in the host population.

Implementing the relationships between \textit{PER} and \textit{ATP} as shown in Figures 2A and S3A into a transmission model requires specifying a maximum \textit{PER} to guarantee the existence of stable equilibriums. Considering this parameter requires refitting the relationships between \textit{PER} and \textit{ATP} as shown in Fig. S5, using the function \( f_1(\text{ATP}) \) (details see legend of Fig. S5), as described in Duerr et al., 2005. To adjust for the observed equilibrium parasite burdens (\( w^* = 40 \) adult female parasites) at very high \textit{ABR}s as in Duerr et al. 2005, we set \( c = 12 \), and use remaining parameter values as listed there (as in Fig. 3b there, we refer to the case of limitation in the microfilarial density and non-regulation in vectors).

With these parameters, the transmission model produces \textit{TBR}s of 80 and 115 bites per person per year for the hypotheses of no intra-host regulation (Fig. S5A) and of facilitated parasite establishment within the human host (Fig. S5B), respectively. These predictions, however, should be regarded as crude estimates only, because (i) The estimate of the \textit{TBR} critically depends on the initial slope of the relationship between \textit{PER} and \textit{ATP} which starts at \( \text{PER} = 0, \text{ATP} = 0 \). The estimated values for this slope, however, are weakly data-based and rely on extrapolating the assumed relationship \( f_1(\text{ATP}) \) towards \( \text{ATP} = 0 \) (see legend to Figure S5). Clearly, a precise determination of the \textit{TBR} requires better data from regions with very low endemicity (see Discussion). (ii) Our simplified transmission model does not take into account factors like host age, heterogeneities, etc., which could also modify the persistence patterns of an infection.
Figure S5: Relationships between the ATP and the PER under both hypotheses, i.e. the PER under no intra-host regulation (A) and the PER₀ under facilitated parasite establishment within the human host (B). The solid curves show fits as represented in Figures 2 and S3. The dashed curves have been implemented into the transmission model, requiring the assumption of an upper limit, \( \lambda_0 \), and using relationships refitted by the function 
\[
 f_0(A TP) = \lambda_0 \frac{\alpha \ Log_{10}(ATP + 1)}{1 + \alpha \ Log_{10}(ATP + 1)}.
\]
\( \lambda_0 \) is assumed to be given by the maximum observed PER (village Be399, see Table 1) and is represented by the dashed line at \( PER = 0.56 \). The estimates are \( \alpha = 0.54 \) in A, and \( \alpha = 1.44 \) in B.
Literature

1 Ross, R. (1911) *The prevention of malaria*, John Murray.
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