Strategic Spatiotemporal Vaccine Distribution Halves Deaths due to an Infectious Disease

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Covid-19 has caused hundreds of thousands of deaths and an economic damage amounting to trillions of dollars, creating a desire for the rapid development of vaccine. Once available, vaccine is gradually produced, evoking the question on how to distribute it best. While official vaccination guidelines largely focus on the question to whom vaccines should be provided first (e.g. to risk groups), here we propose a generic strategy for their distribution in time and space, which sequentially prioritizes regions with a high local infection growth rate. To demonstrate this strategy, we develop an agent-based model describing the time-evolution of infection patterns and their response to vaccination. For heterogeneous infection patterns, the proposed strategy at least halves the number of deaths in our simulations compared to the standard practice of distributing vaccines proportionally to the population density. This applies for a wide range of reproduction numbers and vaccine production rates and might stimulate discussions on the importance of the spatiotemporal distribution of vaccines for official guidelines.

Introduction

The Covid-19 pandemic 2019/2020 [1–5] has led to more than 3 million infections and 200,000 deaths worldwide (early May 2020) [6] and an unprecedented social and economic cost which comprises a sudden rise of the unemployment rate by about 30 million in the USA alone, and a damage of trillions of dollars at the stock market and in the worldwide real economy. This situation challenges politicians to decide on suitable measures and researchers to explore their efficiency, based on models allowing to forecast and compare the evolution of infectious diseases (like Covid-19) when taking one or the other action.

Available measures to efficiently deal with epidemic outbreaks at low infection numbers include a rigorous contact-tracing (e.g. based on “Corona-Apps” [8]) and testing combined with quarantine of infected individuals [9–12]. Strict travel restrictions preventing an infectious disease from entering disease-free regions (or to die out locally [13]) present an alternative measure [14, 15], whereas travel reductions by less than 99% [16] slow down the spreading of the disease only slightly [17]. At higher infection numbers reducing the contact rate through measures broadly affecting a population’s everyday life, such as social distancing [10–12, 19–22] and lockdown [12, 23], remains as the only possibility to avoid an explosion of infection numbers. Unless a population persistently reduces the contact rate to the point where infection numbers decrease (this requires a contact reduction by > 60% for a basic reproduction number of \( R_0 = 2.5 \) [21]), at such stages it has to accept that the majority of its members has to endure the disease – until finally reaching herd immunity [24].

The main hope which remains at such stages rests on the rapid discovery and admission of vaccine [25] to accelerate reaching herd immunity. However, while every day where an infectious disease like Covid-19 is active may cause thousands of additional deaths, even after admission, it may take months until sufficient vaccine is available to overcome an infectious disease. Therefore it is important to strategically distribute the available vaccines such that the number of deaths remains as small as possible. Surprisingly, both official vaccination guidelines, e.g. for pandemic influenza [26, 27], and previous works on vaccine distribution [28–30], focus on the question to whom vaccine should be mainly provided, e.g. to prioritize individuals by age or disease risk, and leave the quest for a suitable spatial and temporal vaccine distribution aside. This results in the common practice of simply distributing vaccines proportionally to the population density [31].

In the present work we propose an alternative strategy for the spatiotemporal distribution of gradually produced vaccines, which hinges on the idea that the number of deaths due to a spreading infectious disease is controlled by the pattern of local infection rates, not by population density. This strategy, which we call the "focusing strategy", sequentially prioritizes regions (cities) with the highest growth rates of the local infection numbers (see Fig. 1 and the supplementary movie) and provides, or "focuses", all available vaccines to those regions. To compare the focusing strategy with the standard “demographic” vaccine distribution practice, we develop an agent-based model describing the time-evolution of an epidemic outbreak (such as Covid-19) and its response to vaccination. As our central result, we find that the number of deaths resulting from infections occurring after the onset of vaccine production is generally smaller when following the focusing strategy rather than the demographic distribution practice. In fact, for heterogeneous infection patterns, the focusing strategy reduces the number of deaths by more than a factor of two, for a large range of...
basic reproduction numbers $R_0$ and vaccine production rates. The difference is largest for $R_0 \sim 2-3$, as typical for Covid-19, but even for $R_0 \sim 1$ and in the presence of additional social distancing rules the focusing strategy significantly increases the survival probability.

To explore the impact of the spatiotemporal vaccine distribution on the disease-evolution in detail, we now introduce a computational model. This model describes the dynamics of $N$ agents moving randomly in continuous space in a box of size $L \times L$ with periodic boundary conditions. The agents represent groups of individuals and have an internal state variable, which is inspired by the SIR model [32,34] and its variants [35,38]. We use colors (see legend in Fig. 1) to represent the possible states in our simulations, which refer to individuals which are “susceptible” (grey), “infected with weak symptoms” (orange), “infected with significant symptoms” (red), “recovered” (green) and “vaccinated” (blue). Infected agents (orange and red) have an inner clock; they remain symptom free for a latency time $t_l$, and then show mild (orange) or significant (red) symptoms for a duration $t_D - t_L$. After an overall disease duration of $t_D$ they either recover with a survival probability $s_{o,r}$ (green) or die with probability $1 - s_{o,r}$ (black), where the indices refer to agents with mild (orange) and significant symptoms (red), respectively. To model the infection dynamics we describe the spatial motion of an agent with position $\mathbf{r}_i(t)$ using Brownian dynamics $\mathbf{r}_i(t) = \sqrt{2D}\mathbf{\eta}_i(t)$, where $D$ is the diffusion coefficient controlling how fast agents move and $\mathbf{\eta}_i(t)$ represents Gaussian white noise with zero mean and unit variance. We assume that all infected agents (orange and red) are infectious, both in the latent phase and afterwards (as for Covid-19) and infect a fraction of $\beta_s + \beta_i$ of those susceptible agents (grey) which are closer than a distance $R_c$; here, indices refer to mild (orange) and significant (red) symptoms. Agents showing significant symptoms (red) do not move but can infect “visitors” if actively approaching them.

![Schematic illustration of the proposed spatiotemporal vaccine distribution strategies and of the simulation model.](image)

FIG. 1: Schematic illustration of the proposed spatiotemporal vaccine distribution strategies and of the simulation model. a) shows the standard “demographic strategy”, where vaccines (dosage needles) are continuously distributed among all regions (e.g. cities) proportionally to their population density (dots represent groups of individuals). b) shows the “infection weighted” strategy, where vaccines are distributed proportionally to the local infection rates (red and orange dots) and c) shows the “focusing strategy” where at early times (clocks) only the region with the largest infection rate receives vaccines until the growth rate of a second region catches up and also receives vaccines. d) shows a typical simulation snapshot for a city size distribution following Zipf’s law taken 42 days after the onset of vaccination when following the focusing strategy. The legend below a)-c) shows the states in our model.

We now perform Brownian dynamics simulations [39–44] starting with $2 \times 10^{-3}N$ randomly distributed initial infections and an initial reproduction number $R_0 = 2.5$ such that infection numbers exponentially increase over time. Let us assume that vaccine production starts after some initial transient and then allows to transfer $\nu$ individuals per day from the susceptible to the immune state. (Note that the duration of the initial transient is unimportant in our simulations, if vaccination starts long before herd immunity is reached.) Now considering the time-evolution of the percentage of infected, dead and recovered individuals of a given population, and distributing the available vaccines proportionally to the population density (bronze curves in Fig. 2), we observe an infection maximum (panel a) about 30 days (two infection cycles) after the onset of vaccine production, i.e. when about 22% of the population have received vaccines and about 2% of the population is infected. When distributing the available vaccines proportionally to the local infection rate (“infection weighted strategy”) instead, notably, the infection maximum occurs an entire infection cycle earlier (silver curve in panel a). Here the infection number peaks when only 11% of the population has received vaccines and only 1% is infected. However, the infection weighted strategy is not optimal but can be further improved by exclusively providing all available vaccines to the region (e.g. a city) with the highest infection rate (“focusing strategy”). This means that initially only a single region receives vaccines until the infection rate of a second region catches up and both regions simultaneously receive vaccines, until a third region catches up and so on. Following this “focusing strategy” the infection peak further shifts to earlier times (golden curve in panel a) and occurs when only 0.6% of the population is infected. Importantly, the resulting fraction of deaths reduces by more than a factor of two when following the infection weighted strategy (silver) rather than the demographic strategy (bronze). It almost halves again when follow-
without vaccination demographic infection weighted focusing without vaccination demographic infection weighted focusing vaccinations

14 140 126 112 98 84 70 56 42 28

Date (days)

0 -0.2 -0.4 -0.6 -0.8

Infections (%)

Deaths (%)

Recoveries (%)

FIG. 2: Competition of spatiotemporal vaccine distribution strategies regarding the time evolution of the fraction of infected individuals (a), the fraction of deaths (b), and of recoveries and vaccinations (c). Dashed red lines show simulation results without vaccination and bronze, silver (or grey) and gold show results for the demographic vaccine distribution strategy, the infection weighted strategy and the focusing strategy respectively. The blue line in panel c) shows the vaccinated fraction of the population and vertical blue lines mark the onset of vaccination; the specific time of which is unimportant (see text). Panels on the right show simulation snapshots taken 14 days after the onset of vaccine production; insets magnify extracts of these snapshots. Parameters: Disease duration \( t_D = 14 \text{days} \); latency time \( t_L = t_D/3 \), survival probability \( s_r = 0.965, s_o = 0.99 \), vaccination rate \( \nu = 0.1 N/t_D \) and initial reproduction number \( R_0 = 2.5 \). (The latter is based on \( D = 10^2 R_0^2/t_D \), \( \beta_o = 0.3 \), \( \beta_r = 0.1 \); see Methods); \( L = 500R_c \); curves are averaged over 100 random initial ensembles with \( N = 6000 \).

To systematically explore the robustness of these findings we now repeat our simulations for different vaccine production rates and initial reproduction numbers. Fig. 3 shows that the resulting fraction of deaths, counted once the disease is gone, is generally highest for the demographic strategy (bronze) and lowest for the focusing strategy (gold). Mathematically, this is because vaccination is most efficient at locations where it maximally reduces the infection growth rate, which holds true independently of the specific parameter regime. The differences among the individual strategies is comparatively large if vaccine is produced fast enough to allow vaccinating at least about 1% of the population per day and at reproduction rates around \( R_0 \sim 2 - 3 \). The latter value might be sensible for Covid-19. However, even for slower vaccine production or for \( R_0 \sim 1 - 2 \) (as typical for influenza), several percent of deaths can be avoided in our simulations by strategically distributing the available vaccines in space and time.

To further explore the applicability-regime of the focusing strategy, we now combine it with social distancing rules, which reduce the reproduction number to \( R \sim 1 \).
We implement the latter as a repulsive three-body interaction among the agents (see Methods for details) which prevents them from aggregating in groups of more than two individuals. Also here, the resulting deaths fraction (Fig. 4[a]) saturates significantly earlier when following the focusing strategy (gold) rather than the demographic strategy (bronze). The difference in deaths numbers among the three different vaccination strategies is almost identical to our corresponding results at $R \sim 1$ but without social distancing (Fig. 3[b]).

Finally, we explore a possible impact of a nonuniform population distribution (city structure) on the proposed vaccination strategies. We create a population with a spatial density distribution following Zipf’s law which closely describes the city size distribution in most countries as $\tilde{P}_c(s > S) \propto 1/S$, where $\tilde{P}_c(s)$ is the probability that a city is larger than $S$. To generate a population featuring a corresponding population distribution, we add an external potential $U$ to the equation of motion of the agents (see Methods for details). Following statistical mechanics, the resulting population density follows Boltzmann’s law $P(r) \propto \exp[-U(r)/(kT)]$ where $P(r)$ is the probability that an agent is at position $r$ and $kT = \gamma D$ is the effective thermal energy of the agents, controlling how often agents leave a “city” (minimum of $U$). Now matching Boltzmann’s distribution with Zipf’s law yields a construction rule for $U$ (see Methods) to create a population pattern featuring a characteristic city-size distribution. Our resulting simulations, shown in Fig. 4[b], and in the supplementary movie (for $N = 55,000$ agents), demonstrate that the focusing strategy and the infection weighted-strategy again halve the number of deaths compared to the demographic strategy. Here, the former two strategies are comparatively close to each other regarding the number of resulting deaths, which indicates that in strongly inhomogeneous populations a suitable spatial vaccine distribution rule might be even more important than the precise temporal sequence of vaccine donation.

**Conclusions** Our simulations suggest that a strategic spatiotemporal distribution of gradually produced vaccines generically increases the number of survivors in ongoing epidemic disease. In particular, by sequentially prioritizing spatial regions (cities) with the highest local infection growth rates, the proposed “focusing strategy” reduces the number of deaths by more than a factor of two compared to the standard practice of distributing vaccines demographically. Such a strong difference occurs for a large range of initial reproduction numbers ($R_0 \sim 1.5 - 4$) and vaccine production rates and even in combination with additional social distancing measures, if the underlying infection pattern is sufficiently heterogeneous and vaccine production starts long before the population reaches herd immunity. Our results might inspire a variety of disease-specific future modelling works incorporating large-scale data analyses to further test the proposed strategy. They might also serve as useful background information for advising politicians and

![FIG. 4: Competition of spatiotemporal vaccination strategies](image-url)

...could excite discussions regarding the importance of the spatiotemporal distribution of gradually produced vaccines for official vaccination guidelines.
Methods

Simulation details:
To calculate the spatial dynamics of the agents in our model, we solve Langevin equations \( \dot{r}_i(t) = \sqrt{2D}\eta_i(t) \) with \( i = 1, \ldots, N \) using Brownian dynamics simulations involving a forward Euler time-stepping algorithm and a time-step of \( dt = 0.0028 \) days which amounts to about 4 minutes. After each timestep we check for each infected agent (red or orange) which susceptible agents (grey) are closer than \( R_c \). We then change the state of the latter agents to an infected state with an infection rate of \( \beta_o = 3\beta_r = 0.0075/dt \) (Figs. 2-4a), corresponding to infections with mild symptoms (orange) and significant symptoms (red), respectively. These rates yield \( \beta_o = 3\beta_r = 0.3 \) for the corresponding fractions of contacts which lead to infections.

City size structure:
To generate a population density distribution with a structure which is typical for cities, we add an external potential landscape \( U(r) \) to the Langevin equations describing the dynamics of the agents, i.e. \( \dot{r}_i(t) = \sqrt{2D}\eta_i(t) - \nabla_r U(r_i)/\gamma \). Here \( \gamma \) is an effective “drag” coefficient determining the strength of the response of the agents to \( U \). We now create \( U \) as a superposition of Gaussians, \( U(r) = \sum_j a e^{-\frac{(r-r_j)^2}{2\sigma_j^2}} \), each of which leads to a population density maximum around \( r_j \), which represents the center of city \( j \). Here \( a \) is the strength (amplitude) of the reduced potential which we choose as \( a = D\gamma/2 = kT/2 \) and \( \sigma_j \) defines the radius of city \( j \), which we choose randomly from a distribution \( P(R) = \frac{1}{\pi \ln(R_{\text{max}}/R_{\text{min}})} \) where \( R_{\text{min}} = 20R_c \) and \( R_{\text{max}} = 80R_c \) are the minimal and the maximal possible “city radius” in the simulations underlying Fig. 4b. We randomly distribute the city centers \( r_j \) within the simulation box.

Social distancing:
To model social distancing, we add repulsive excluded volume interactions among the agents which prevent that groups of more than two agents form. That is, we choose \( U = \frac{1}{2} \sum_{k,l \neq k} V_{kl} \nu_{kl} \) where the sums run over all agents and where \( V_{kl} \) represents the Weeks-Chandler-Anderson interaction potential among agents \( k,l \), i.e. \( V_{kl} = 4\epsilon \left[ \left( \frac{d}{r_{kl}} \right)^{12} - \left( \frac{d}{r_{kl}} \right)^{6} \right] + \epsilon \) if \( r_{kl} \leq 2^{1/6}d \) and \( V_{kl} = 0 \) otherwise. Here \( r_{kl} \) denotes the distance between agents \( k \) and \( l \) and \( r_{\text{cut}} = 2^{1/6}d \) represents a cutoff radius beyond which the interaction potential is zero; \( \epsilon \) controls the strength of the potential and is chosen such that \( \epsilon/\gamma = D \). In our simulations at each timestep we choose \( \nu_{kl} = 1 \) if at least one of the agent \( k \) and \( l \) has a “neighbor” at a distance closer than \( d = 3R_c \) and otherwise we choose \( \nu_{kl} = 0 \). In addition, we add a weak pair attraction of strength \( D/10 \) and range \( d = 3R_c \) to our simulations to support the formation of pairs. That way, agents can form pairs but there is a significantly reduced probability that they form triplets or larger groups.

Relation of reproduction number to simulation parameters:
Here we relate the reproduction number \( R \), which is the average number of infections caused by an infected agent, with the microscopic parameters in our simulation. For this purpose, let us first consider the area \( A(t) \) covered by a Brownian agent with radius \( R_c \) and diffusion coefficient \( D \) over a time \( t \). This area is known as the Wiener sausage [46] and reads
\[
A(t) = \pi R_c^2 + \frac{8R_c^2}{\pi} \int_0^\infty \frac{1 - e^{-\frac{2Dd^2t}{\pi R_c^2}}}{y^3} J_2^2(y) \, dy ,
\]
where \( J_0(y) \) and \( Y_0(y) \) are the 0-th Bessel functions of the first and second kind. Now denoting the agent density of susceptible agents with \( \rho_S \), the average number of (possibly infectious) contacts during a time \( \tau \) is \( A(\tau)\rho_S \). Thus, if agents are infectious over an overall time of \( t_D \) and the fraction of contacts which lead to infections with significant (mild) symptoms is \( \beta_r \) (\( \beta_o \)), we obtain the following expression for the (spatially averaged) reproduction number:
\[
R(t) = A(t_D)\rho_S(t) (\beta_o + \beta_r) .
\]
This expression links the reproduction number with the microscopic simulation parameters and reveals that the reproduction number at time \( t \) is proportional to the average density of susceptible agents at time \( t \).

Continuum theory:
Here we formulate a continuum theory of our agent-based model. Integrating this model, e.g. by using finite difference simulations allows us to test the spatiotemporal vaccination strategies at the continuum level. This is particularly useful to study very large length and timescales. The continuum description is based on equations of motion for continuous variables (fields) representing the mean number density of susceptible agents \( S(r,t) \), exposed agents \( E(r,t) \) (infected but not yet diseased), infected agents which are free of symptoms (or have mild symptoms) \( F(r,t) \), infected agents with symptoms \( I(r,t) \), and recovered (immune) agents \( G(r,t) \):
agents have an inner clock and are in the latent phase before showing (mild) symptoms. In the above equations, $\beta'$ is the infection rate, i.e. $1/\beta'$ is the mean time between infectious contacts; $\alpha = 1/t_L$ is the rate to switch from the exposed (latent) state to the infected state, $\delta = 1/(t_D - t_L)$ is the recovery rate and $\nu'(r,t)$ is the spatiotemporal vaccination rate which is linked to the constant vaccination rate in the agent-based model via $\nu = \int \mathrm{d}r \nu'(r,t)$. The number $r$ is the ratio of infections proceeding symptom free (or with mild symptoms) and $\rho_0 = N/L^2$ is the mean agent density. Finally, $D$ is the diffusion coefficient and $f(r) = -\nabla'_r U/\gamma$ is the reduced force due to the external potential which we use to create a density profile mimicking a typical city size distribution. The overall density converges to a Boltzmann distribution $S + E + F + I + G = N \exp\left[-U(r)/(kT)\right]/\int \exp\left[-U(r)/(kT)\right]\mathrm{d}r$, yielding the conservation law $\int (S + E + F + I + G) \mathrm{d}r = N$ which can be viewed as an expression of the conservation of the overall number density (or the number of agents) in the coarse of the dynamics. We have simulated this model using the finite difference method, starting with the initial state $E = F = G = 0$ and $S = 1 - \epsilon$, $I = \epsilon$ where $\epsilon(r,t)$ represents a small perturbation of the unstable steady state $E = F = G = I = 0$, $S = 1$ which represents the population before the emergence of the disease. The results of these simulations confirm that the spatiotemporal distribution of continuously distributed vaccines plays an important role; also here, the infection-weighted strategy and the focusing strategy strongly increase the number of survivors as compared to the demographic distribution.

Supplementary Movie: The movie shows the time-evolution of the modeled infection pattern for $N = 55,000$ agents and its response to the proposed spatiotemporal vaccine distribution strategies. Parameters are as in Fig. 4b and the population distribution in the movie follows a typical city size structure (Zipf’s law).

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