

The importance of saturating density dependence for predicting SARS-CoV-2 resurgence

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is transmitted more effectively in densely populated areas and omitting this phenomenon from epidemiological models may substantially affect projections of spread and control. Adjusting for deprivation, proportion of ethnic minority population and proportion of key workers among the working population, mortality data from England show good evidence for an increasing trend with population density until a saturating level. Projections from a mathematical model that accounts for this observation deviate markedly from the current status quo for SARS-CoV-2 models which either assume linearity between density and transmission (30% of models) or no relationship at all (70%). Respectively, these standard model structures over- and under-estimate the delay in infection resurgence following the release of lockdown. Models have had a prominent role in SARS-CoV-2 intervention strategy; identifying saturation points for given populations and including transmission terms that account for this feature will improve model utility.

Introduction

Like many pathogens that cause respiratory diseases (1-3), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appears to be transmitted more effectively in densely populated areas (4-6). Although evidence is mounting for density-dependent SARS-CoV-2 transmission, no nationwide assessment has yet been conducted. The increased disease rates reported among high-density populations (4, 5, 7, 8) may, for example, be an artefact of confounders such as the higher proportion in urban areas of individuals of lower socioeconomic status or from minority ethnic groups (9). Using COVID-19 associated mortality data from the Office for National Statistics we aimed to assess the evidence for density dependence.

Standard transmission models that either do or do not account for this density dependence are used interchangeably because their projections are generally equivalent when population density remains unperturbed. While the ~1% infection fatality rate for COVID-19 (10) is insufficient to destabilize populations, the reaction of most countries' governments to curtail disease spread through mass quarantine ('lockdown') and social distancing has had unprecedented impacts on the density of mobile human populations. For example, the UK's lockdown, which came into effect on March 23rd 2020, effectively reduced the freely moving population from 66.5 million to 10.6 million (key workers) (11). We evaluate the extent to which models built to inform the epidemiology of COVID-19 use an underlying structure that can accommodate the drastic changes in densities experienced by most global populations.

As lockdowns are gradually released over the latter part of 2020, global populations will equilibrate to a 'new normal' whereby densities are increased but in which contact patterns are expected to remain reduced through social distancing interventions (12). Using a suite of mathematical models we aim to illustrate the impact that the different, routinely ignored, assumptions underlying transmission and density may have in projecting infection dynamics and measuring intervention effectiveness.

Results

Evidence for saturating density dependence in COVID-19 associated deaths

COVID-19 associated deaths are strongly influenced by urbanization level (Supporting Fig 1). Adjusting for potential confounders of deprivation, ethnic distribution and proportion of key workers within the local population via a negative binomial GLM (offset by age-standardized expected mortality in order to estimate the standardized mortality ratio, SMR), a saturating dependence on population density provided the best fit to total local authority mortality rates over the study period, with respect to the leave-one-out information criterion (LOOIC) (Figure 1a). Models independent or linearly dependent on density were very similar since the fitted linear trend was negligibly small, and both performed worse than the log-linear and saturating forms. The chosen model suggests a 3.6-fold (90% CrI [2.44, 5.28]) increase in SMR for a unit increase in density on the saturated scale. Incidental findings suggested strong evidence for an effect of ethnic distribution and deprivation index on observed SMR (90% CrI on standardized covariate: [1.1, 1.2] for % BAME population, and [1.04, 1.13] for IMD score), but not of the proportion of key workers (90% CrI [0.95, 1.03]).

Under the saturating density-dependent model, the impact of lockdown on reducing transmission and deaths is heterogeneous - having greatest benefit to regions with low population density (>30% reduction in projected deaths for example in Dorset, Herefordshire and the Derbyshire Dales) but reduced benefit to high-density regions (~7-8% reduction for the London boroughs of Tower Hamlets, Hackney, Islington and Camden) (Fig 1b).

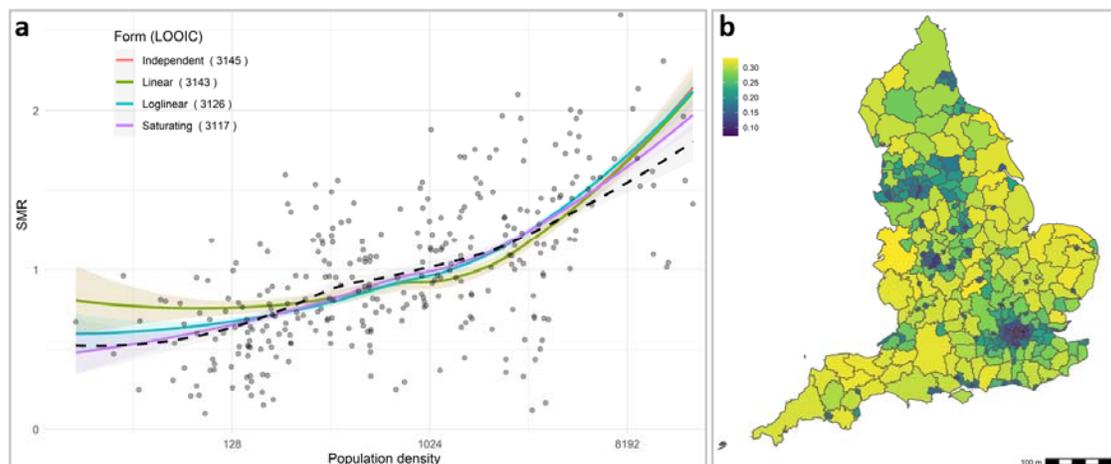


Fig 1. Dependence of standardized mortality rate (SMR) on population density. a) Four forms of density dependence are illustrated in the left panel, with LOOIC values for each fit demonstrating superiority of the saturating density-dependent function. **b)** The heterogeneous impact of 84% effective density reduction on predicted deaths according to the saturating model is mapped in the right panel.

Projecting SARS-CoV-2 resurgence after lockdown is released

A full text review of 100 epidemiological models of SARS-CoV-2 showed that 70% explicitly assume that contact rate between people (and, hence transmission) is unaffected by population density

(Supporting Information). Of the remaining 30% of models, all assumed a linear relationship between population density and transmission.

We use a metapopulation model to simulate the infection dynamics among freely moving as well as locked-down individuals, incorporating transmission terms that can accommodate frequency-dependent as well as linearly and saturating density-dependent assumptions. We show that while all functional forms perform equivalently in fitting mortality data leading up to lockdown, dynamics under alternate assumptions may diverge markedly during and following the phase when lockdown is released (Fig. 2). We note that any adaptive public health responses (i.e. additional interventions) curbing the second wave are ignored - this comparison is intended to illustrate the consequences to projected dynamics of alternative assumptions underlying density and transmission.

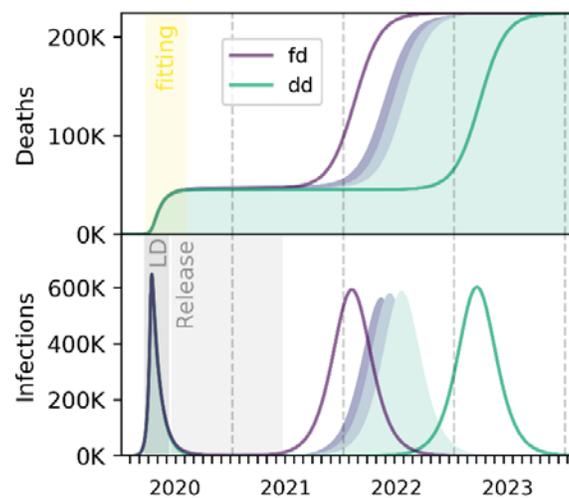


Fig. 2. Population density and SARS-CoV-2 dynamics. COVID-19 associated mortality (top) and infection dynamics (bottom) following the release of lockdown 'LD' under the three different transmission terms (frequency-dependent 'fd', linearly density-dependent 'dd' and saturating density-dependent). Lighter filled areas illustrate saturating density-dependent dynamics for lower population density (where England's density is set to equal that of London at 5700 people per Km^2 , the average English population density at 430 people per Km^2 or Cornwall at 160 people per Km^2). These simulations show a 1-year release of locked down individuals and infection preventative behaviors (e.g. face masks) that halve the per contact transmission rate. Details of model-fitting are in the supplementary materials.

Although final epidemic size and total deaths were the same for the alternative classic assumptions, transmission was delayed by over a year under a density- versus frequency-dependent model (Fig 2). This delay occurs because only under the density-dependent assumption the force of infection is reduced while any part of the population remains locked down. At the very high densities of London populations, locking down 84% of people under our saturating density-dependent model had an impact most similar to a frequency-dependent assumption. Meaning, were England's population equivalent to the density found in London, infection dynamics and deaths resulting from a saturating density-dependent model most closely match the frequency-dependent projections (with a 3-month lag). However, London has a population density that is an order of magnitude higher than the next most populated region in England; and projected infection dynamics diverged more considerably

under scenarios reflecting densities experienced outside of the capital. The force of infection and the timing of peak prevalence for the saturating density-dependent model is constrained between the frequency- and linearly density-dependent versions (13) with lower densities tending towards the latter.

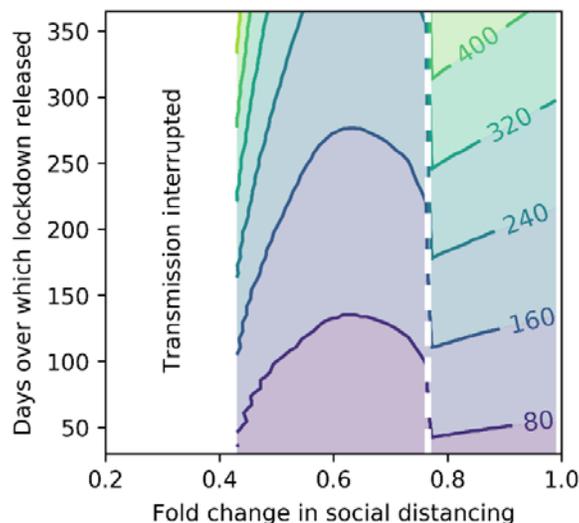


Fig. 3. Consequences of density dependence on intensive care unit inundation. Difference (in days, contours) between models in their projected time before ICU capacity is exceeded, as a function of lockdown release schedule and effectiveness of social distancing. The dashed white line marks minimum social distancing required to prevent immediate ICU inundation under the frequency-dependent model.

Assuming a maximum capacity of 5000 intensive care units (ICU), we then assess the difference between these temporal limits in the projected duration between the release of lockdown and a second wave of infection exceeding ICU capacity (Fig. 3). Threshold levels of social distancing to interrupt transmission (i.e., maintain effective reproduction number below one) are similar for both classic models. However, where interventions fail to achieve this threshold, density-dependent transmission may delay ICU inundation by a year. This is contingent on the timeframe across which lockdown is released, whereby more gradual releases extend delays.

Discussion

Projections of COVID-19 infection dynamics following the release of a huge proportion of the population from lockdown comprise an urgent and critical component of public health decision making (14). The classical forms of modelling infectious diseases among populations have been used interchangeably by different research groups because, under most plausible circumstances, they exhibit equivalent dynamics. In March 2020, England locked down over 80% of its population. For most, this fundamentally altered the rate at which people made contact with each other. Under the current circumstance of millions of people easing out of lockdown, substantial differences between projections from a frequency- and density-dependent transmission assumption emerge. Most notably, density dependence delays infection resurgence; and, contingent on the timeframe across which lockdown is released, and the effectiveness of social distancing, this delay can extend to over a year.

The delay is a function of a fundamental aspect of density-dependent transmission: lower host densities reduce the force of infection and there is a threshold host density below which an infection cannot spread. Despite its origins in human infectious disease modelling (15), the existence of this threshold has historically had limited epidemiological applications. The phenomenon is discussed more widely in wildlife disease ecology (16) where it underlies key disease-control decisions such as culling (17). Current expectation is that lockdowns, either full or of a more moderate or localized form, will be reimplemented when cases restart increasing. Density effects and thresholds are particularly pertinent in the current pandemic during which extreme fluctuations in mobile human density are likely to continue.

Analyzing COVID-19 associated deaths across different regions in England, and accounting for known, major confounders (9), the non-linear increase in deaths with population density was adequately captured by neither classical form of modelling transmission. Using a function that captures the saturating increase in deaths with population density resulted in an expedited resurgence compared with a linearly density-dependent model and a delayed resurgence compared with the popularly used frequency-dependent model.

Less populated areas were shown to have fewer per capita deaths (as per England's mortality data) and slower resurgences following the release of lockdown. This provides more achievable targets and considerably more lead time for health services to prepare than would otherwise be anticipated. It also highlights a hazard. During and after releases from lockdown, in order to fit a prolonged lag in cases, transmission rates derived from most current (frequency-dependent) models will underestimate the effective reproduction number. This could mislead assessments of the effectiveness of ongoing interventions, such as social distancing or face masks, with potentially serious consequences.

Our study is limited by the fact that we do not have comprehensive data on how contact rates were affected prior to and over the lockdown period for individuals inhabiting regions of differing population density. Instead we have had to resort to mortality rates as a proxy. It is possible, for example, that contact rates are not affected by dramatic shifts in population density regardless of

baseline levels (i.e., the average England resident came into contact with as many individuals during lockdown as prior to lockdown, satisfying a frequency-dependent assumption), and that the increased per capita fatality seen in more densely populated regions has an alternative, thus far unidentified explanation. Mobile phone applications developed to inform participants of urgent health information have already gained millions of users in the current coronavirus context (18). Piggy-backing on these efforts could help substantiate the evidence for the contact-density relationships we have identified.

Infectious diseases are emerging at an unprecedented rate (19) and the upwards trend in global travel and urbanization increases the likelihood of pandemics (20). Their success in controlling SARS-CoV-2 means that widescale lockdowns will not only continue to be enforced as this pandemic progresses, but they will likely be more readily applied in future emergencies. It is crucial that we use the current opportunity to collect data to inform more precise forms of how contact rates are altered at varying stages of lockdown. Incorporating realistic contact-density relationships into the transmission term of population-level mathematical models will improve precision of their projections and their utility in public health decision making.

Materials and Methods

Data

Reported COVID-19-related deaths between the 20-03-2020 and 29-05-2020 were obtained from the Office for National Statistics (ONS), including all cases where COVID-19 is either mentioned or named as an underlying cause (N = 43,288). Individual records were aggregated to lower-tier local authority (LTLA). Records which did not have a LA provided (n = 74) were excluded, along with any with age less than one year (n = 3), due to lack of population estimates for this age group.

Local authority shapefiles and single-age population estimates were also obtained from ONS (21). Four sub-regions of Buckinghamshire (Aylesbury Vale, Chiltern, South Bucks, Wycombe) were aggregated in order to match most recent population estimates. The City of London was aggregated with Westminster due to its very small resident population, and the Isles of Scilly excluded since no COVID-19-related deaths had been reported there during this period. Population density was estimated from the total LTLA population estimate divided by the corresponding shape file area in km². Index of multiple deprivation (IMD) (22), percentage of minority ethnic population (23) and percentage of key workers among the working population (24) are characteristics of the LTLA population potentially associated with both COVID-19 mortality and population density, therefore were included as covariates in all models. Percentage of key workers was missing for Westminster and Cornwall; these were imputed by the median value across all bordering LTLAs.

Statistical analysis

Expected deaths per local authority were calculated according to national age-specific rates applied to local population estimates in ten-year age bands. Negative binomial regression models were then fit to the age-standardized mortality ratio (SMR = observed/expected) via inclusion of expected deaths as an offset, adjusting for the three covariates (IMD, % minority population and % key workers). Population density was accounted for in one of four functional forms:

- A. Constant/independent of population density
- B. Linear
- C. Log-linear
- D. Saturating

Models were fit using the `rstanarm` package (25) for straightforward implementation of a Bayesian regression framework, with default weakly-informative priors. The four model variants were compared on expected log predictive density (elpd), calculated via approximate leave-one-out cross validation as implemented in the `loo` package (26). The value of theta for the saturating function was determined by manual optimization of the glm with respect to elpd over a range from 0.01 to 1, initially in steps of 0.1 and then iteratively finer between a smaller range either side of the maximum reached.

For the saturating model, the impact of 84% reduction in effective population density as a result of lockdown on predicted mortality was calculated as a percentage change between mean model-predicted deaths under the original and reduced densities.

Mathematical model

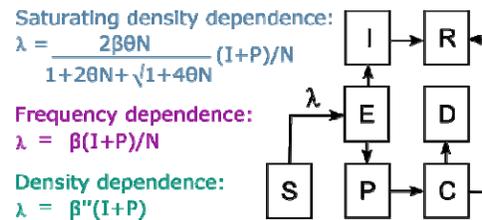


Fig. 4. Model compartments and alternative transmission assumptions. Model compartments are: ‘S’usceptible, ‘E’xposed, ‘I’nfected, ‘P’re-critical infectious, ‘C’ritically ill, ‘D’ead and ‘R’ecovered. Under a frequency-dependent assumption, the force of infection, λ , is the product of the transmission coefficient, β , and the proportion of the total population, N , that are infectious. Under a density-dependent assumption, the force of infection is a product of the transmission coefficient and the density of infectious individuals. The saturating density-dependent formulation assumes the force of infection is a product of the transmission coefficient and a function of the density of infectious individuals and parameter θ derived from analyzing England’s regional mortality data.

We use a discrete-time, deterministic compartmental model (Fig. 4) with daily timesteps to simulate SARS-CoV-2 transmission. From the first day of lockdown (March 23rd 2020), 84% of the population enter quarantine in which frequency-dependent transmission occurs. This assumption is made for the lockdown sub-population because an individual’s likelihood of contracting infection while in their home is limited by their household size (i.e., not impacted by the density of individuals under quarantine in different households). Each model is fitted independently to England’s COVID-19 associated mortality data (up until August 1st 2020). We compare frequency-dependent and both linearly and saturating density-dependent transmission among the remaining free-movers for when lockdown is released. We also explore the impact of varying rates of migration between locked down and free-moving individuals (Supplementary Materials). We compare frequency-dependent and linearly density-dependent transmission (the limiting cases for the saturating density-dependent model) among the remaining free-movers for a range of lockdown release schedules (over a period of between 1 and 12 months). Contact rates are reduced through two distinct mechanisms under the density-dependent models: whereas social distancing among the freely moving population (e.g. the 2-metre rule) is included in all models, only the density-dependent versions assume reduced opportunities for coming into contact with others because of the substantially depleted numbers of mobile people. Full model specification and sources for its parameterization can be found in the Supplementary Materials, and the Python (v3.8) code is freely available from <https://github.com/lwyakob/COVIDsaturates>.

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Acknowledgments

Funding: OJB was funded by a Sir Henry Wellcome Fellowship funded by the Wellcome Trust (206471/Z/17/Z).

Author contributions: LY conceived of the study, reviewed COVID-19 models and performed the mathematical modelling analysis. EN and OJB performed the statistical analysis. All authors contributed towards results interpretations and writing.

Competing interests: There are no competing interests.

Supplementary Materials

Supplementary Materials and Methods

Google Scholar search by year '2020' on June 19th 2020:

coronavirus, OR covid19, OR covid-19 ""(mathematical OR simulation OR transmission) model"

613 results were returned and ordered by relevance. These were scanned to ascertain if they used SIR-related models and whether they declared (either explicitly stating or in presented equations) which functional form of transmission was used in their analysis, until 100 relevant articles were found for inclusion in this review. The following are the list of papers sorted by whether they use density- or frequency-dependent transmission.

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Mathematical model equations

Free-moving subpopulation:

$$\begin{aligned}
 S_t &= S_{t-1} - S_{t-1}(\lambda + \varepsilon)(1 - \phi) - (\phi S_{t-1}) + (\psi S_{L,t-1}^2) + (\kappa S_{L,t-1}) \\
 E_t &= E_{t-1} + [\lambda S_{t-1} - (\alpha + \varepsilon)E_{t-1}](1 - \phi) - (\phi E_{t-1}) + (\psi E_{L,t-1}^2) + (\kappa E_{L,t-1}) \\
 I_t &= I_{t-1} + [(1 - \rho)\alpha E_{t-1} - (\gamma + \varepsilon)I_{t-1}](1 - \phi) - (\phi I_{t-1}) + (\psi I_{L,t-1}^2) + (\kappa I_{L,t-1}) \\
 P_t &= P_{t-1} + [\rho\alpha E_{t-1} - (\nu + \varepsilon)P_{t-1}](1 - \phi) - (\phi P_{t-1}) + (\psi P_{L,t-1}^2) + (\kappa P_{L,t-1}) \\
 C_t &= C_{t-1} + [\nu P_{t-1} - (\mu\tau + \varepsilon + (1 - \mu)\omega)C_{t-1}](1 - \phi) - (\phi C_{t-1}) + (\psi C_{L,t-1}^2) + (\kappa C_{L,t-1}) \\
 R_t &= R_{t-1} + [\gamma I_{t-1} + (1 - \mu)\omega C_{t-1} - \varepsilon R_{t-1}](1 - \phi) - (\phi R_{t-1}) + (\psi R_{L,t-1}^2) + (\kappa R_{L,t-1}) \\
 D_t &= D_{t-1} + \mu\tau C_{t-1}
 \end{aligned}$$

Locked down subpopulation:

$$\begin{aligned}
 S_{L,t} &= S_{L,t-1} - S_{L,t-1}(\lambda + \kappa) + (\phi S_{t-1}) - (\psi S_{L,t-1}^2) + (1 - \phi)\varepsilon S_{t-1} \\
 E_{L,t} &= E_{L,t-1} + \lambda S_{L,t-1} - (\alpha + \kappa)E_{L,t-1} + (\phi E_{t-1}) - (\psi E_{L,t-1}^2) + (1 - \phi)\varepsilon E_{L,t-1} \\
 I_{L,t} &= I_{L,t-1} + (1 - \rho)\alpha E_{L,t-1} - (\gamma + \kappa)I_{L,t-1} + (\phi I_{t-1}) - (\psi I_{L,t-1}^2) + (1 - \phi)\varepsilon I_{L,t-1} \\
 P_{L,t} &= P_{L,t-1} + \rho\alpha E_{L,t-1} - (\nu + \kappa)P_{L,t-1} + (\phi P_{t-1}) - (\psi P_{L,t-1}^2) + (1 - \phi)\varepsilon P_{L,t-1} \\
 C_{L,t} &= C_{L,t-1} + \nu P_{L,t-1} - (\mu\tau + \kappa + (1 - \mu)\omega)C_{L,t-1} + (\phi C_{t-1}) - (\psi C_{L,t-1}^2) + (1 - \phi)\varepsilon C_{L,t-1} \\
 R_{L,t} &= R_{L,t-1} + \gamma I_{L,t-1} + (1 - \mu)\omega C_{L,t-1} - \kappa R_{L,t-1} + (\phi R_{t-1}) - (\psi R_{L,t-1}^2) + (1 - \phi)\varepsilon R_{L,t-1} \\
 D_{L,t} &= D_{L,t-1} + \mu\tau C_{L,t-1}
 \end{aligned}$$

The transmission rate in the absence of any intervention was set according to the final epidemic size assuming an R_0 of 3 (27). Data captured deaths pre-lockdown, during lockdown and just following the initial release of individuals after lockdown. During lockdown, the population split into two sub-populations. The transmission rates were generated by fitting deaths in the model to England's mortality data retrieved from the WHO (28). At the same time as lockdown, social distancing also reduced per capita contact rates among the free-moving population:

$$\sigma = \begin{cases} \text{range}(0.1 - 1) & \text{if } t > \text{lockdown} \\ 0 & \text{otherwise} \end{cases}$$

For the full range of social distancing, the model was refitted to the mortality data (more stringent social distancing among free-movers requiring less of a reduction in the lockdown transmission rate, β_L). Least squares fitting using the Levenberg-Marquardt minimization algorithm was conducted using 'lmfit' in Python v3.8.

Supplementary figures

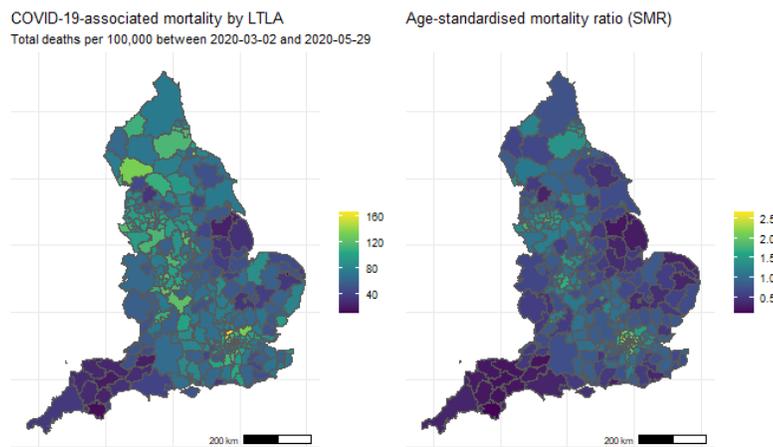


Fig. S1. COVID-19 associated mortality in England. Total rates per 100,000 are mapped in the left panel and age-standardized mortality ratios in the right, by lower-tier local authority.

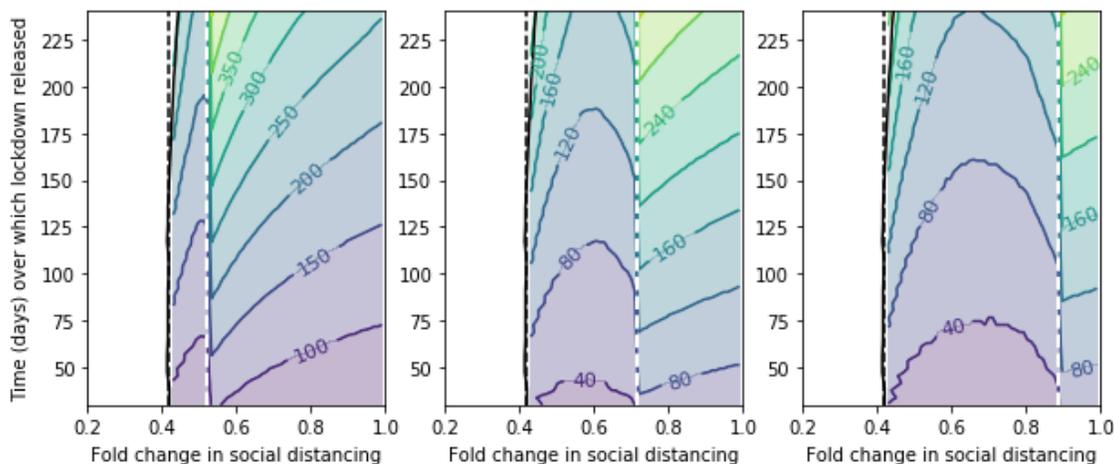


Fig. S2. Sensitivity analysis of movements between sub-populations. The difference between functional forms in projected time (contours=days) until the ICU capacity is exceeded by critically ill patients. Left: 50% movement (ϵ), Middle: 100% ϵ , Right: 150% ϵ . For each value of ϵ the model was refitted to the data (the density-dependent model was insensitive to movement; for the frequency-dependent model, higher rates of movement required slightly less of a reduction in transmission among the lockdown sub-population). Black lines mark thresholds for interrupting transmission for density-independent (dashed) and -dependent (solid) models. Dashed white lines mark minimum social distancing required to prevent immediate ICU inundation under the frequency-dependent model.

Supplementary tables

Table S1. Mathematical model variables

Variable	Definition
$S_t, S_{L,t}$	Susceptible population at time 't'; subscript 'L' denotes lockdown sub-population
$E_t, E_{L,t}$	Exposed population at time 't'
$I_t, I_{L,t}$	Infected population at time 't'
$P_t, P_{L,t}$	Pre-critically infected population at time 't'
$C_t, C_{L,t}$	Critically infected population at time 't'
$R_t, R_{L,t}$	Recovered population at time 't'
$D_t, D_{L,t}$	Dead population at time 't'
<i>free</i>	Total living, free-moving (non-lockdown) sub-population
<i>home</i>	Total living lockdown sub-population

Table S2. Mathematical model parameters

Parameter	Definition	Value	Source
λ	Force of infection (composite of other parameters and variables)	n/a	n/a
β''	Transmission rate (linearly density-dependent assumption)		derived
β	Transmission rate		derived
β_L	Transmission rate while under lockdown (frequency dependent)		derived
ε	Daily rate of movement from free-moving to lockdown sub-pop	See sensitivity analysis section	
κ	Daily rate of movement from lockdown to free-moving sub-pop		
ϕ	Pulsed, mass movement of 84% free-movers into lockdown	0.84	(11)
ψ	Daily rate of release of lockdown sub-pop	Wide range tested	
σ	Fold change in social contacts among free-movers	Wide range tested	
α	Inverse of infection latent period	1/5.8	(29)
ρ	Proportion of infected individuals becoming critically infected	0.02	(30)
γ	Inverse of recovery period	1/5	(31)
ν	Inverse of additional delay before symptoms become critical	1/7	(32)
μ	Proportion of critically infected that die	0.427	(33)
τ	Inverse of time for critically ill to die	1/7	(34)
ω	Inverse of time for critically ill to recover	1/7.2	(33)