Likely effectiveness of pharmaceutical and non-pharmaceutical interventions for mitigating influenza virus transmission in Mongolia


Objective To assess the likely benefit of the interventions under consideration for use in Mongolia during future influenza pandemics.

Methods A stochastic, compartmental patch model of susceptibility, exposure, infection and recovery was constructed to capture the key effects of several interventions – travel restrictions, school closure, generalized social distancing, quarantining of close contacts, treatment of cases with antivirals and prophylaxis of contacts – on the dynamics of influenza epidemics. The likely benefit and optimal timing and duration of each of these interventions were assessed using Latin-hypercube sampling techniques, averaging across many possible transmission and social mixing parameters.

Findings Timely interventions could substantially alter the time-course and reduce the severity of pandemic influenza in Mongolia. In a moderate pandemic scenario, early social distancing measures decreased the mean attack rate from around 10% to 7–8%. Similarly, in a severe pandemic scenario such measures cut the mean attack rate from approximately 23% to 21%. In both moderate and severe pandemic scenarios, a suite of non-pharmaceutical interventions proved as effective as the targeted use of antivirals. Targeted antiviral campaigns generally appeared more effective in severe pandemic scenarios than in moderate pandemic scenarios.

Conclusion A mathematical model of pandemic influenza transmission in Mongolia indicated that, to be successful, interventions to prevent transmission must be triggered when the first cases are detected in border regions. If social distancing measures are introduced at this stage and implemented over several weeks, they may have a notable mitigating impact. In low-income regions such as Mongolia, social distancing may be more effective than the large-scale use of antivirals.

Introduction

The efficient use of resources to mitigate the spread of an emerging infectious disease is of global interest. However, the most appropriate control strategies in any given area probably depend on the nature of the local population and environment. Implementing interventions against emerging infectious diseases is particularly important in developing countries, such as Mongolia, where the capacity to provide health care and undertake detailed surveillance is limited. Since the identification of highly pathogenic avian influenza in Mongolia in 2005, the Mongolian government has been particularly aware of the threat posed by influenza to public health. Mongolia’s vulnerability to influenza was reinforced by the impact on the country of A(H1N1)pdm09. The establishment of A(H1N1)pdm09 transmission in the dense population of Ulaanbaatar probably led to the rapid spread of cases in the capital and the rapid dissemination of the virus to the rest of Mongolia. The epidemic reached a distinct peak in weeks 44–45, when the reports of IILI were dominated by the cases in Ulaanbaatar, although, by then, every aimag except Bayan-Olgii in the far west was reporting more than 50 IILI cases per 10 000 (Appendix A, available at: http://mathmodelling.sph.unimelb.edu.au/publi-
The interventions implemented against influenza virus transmission during the 2009 pandemic were triggered by the detection of elevated IIL activity in Ulaanbaatar in week 42. The first intervention was the closure of primary schools. High schools and kindergartens were also soon closed for a period of several weeks. In week 45, further social distancing measures were imposed in Ulaanbaatar. Restrictions included limiting the opening hours of shops, cafes and restaurants, banning public gatherings and closing markets. Provincial rail and road travel was interrupted for a period of several weeks. In addition to these mandatory social distancing measures, all citizens were advised to minimize activity outside of their homes and to wear facial masks, and symptomatic individuals were encouraged to stay in self-imposed quarantine at home. Institutions and businesses were recommended to supply staff with vitamin supplements to "build health." Although no formal evaluation of public compliance is available, anecdotal evidence indicates that the intervention measures were generally well accepted. Initiatives such as the broadcasting of school lessons on national television probably facilitated compliance.

While the resources and infrastructure deemed necessary for effective epidemic containment by non-pharmaceutical means are probably found in very few settings, less stringent measures may still usefully reduce the burden on acute healthcare services. International borders remained open during the 2009 pandemic in Mongolia. Although border screening was in place in Ulaanbaatar, the first case of A(H1N1)pdm09 infection was detected through the national surveillance network.

The Mongolian government's stockpile of around 80,000 doses of the antiviral drug oseltamivir was exhausted during the 2009 pandemic. Although oseltamivir was taken as prophylaxis by some health-care workers, the drug was predominantly used to treat severe hospitalized cases. The Mongolian government purchased vaccine against A(H1N1)pdm09, which was supplemented by donations from the World Health Organization (WHO). However, vaccine roll-out only commenced in January 2010 after the epidemic peaked.

Here we use the epidemiological data collected during the 2009 influenza pandemic in Mongolia to calibrate a computational model of influenza virus dissemination in a Mongolian pandemic, with tailoring to the country’s infrastructural and sociobehavioural characteristics. We explore the likely impact of various nationwide social distancing and pharmaceutical interventions on mitigating the spread of a pathogen, with particular emphasis on a novel influenza strain with established transmission in the human population. Earlier country-specific evaluations of the likely impact of interventions on influenza have focused on the containment of highly pathogenic avian influenza outbreaks in south-eastern Asia and the United States of America. There have been few recent, country-specific evaluations of strategies for the mitigation of influenza, particularly in resource-poor settings. Our results provide novel insights into the probable benefits of anti-influenza interventions in Mongolia, some of which are potentially relevant in pandemic planning in other low-income regions.

Methods

Modelling transmission during interventions

Influenza transmission was explored using a stochastic, computational model of susceptibility, exposure, infection and recovery. Large-scale spatial transmission was captured by geographically dividing the population into 14 patches chosen to isolate border crossings, sentinel surveillance sites, urbanized regions and other regions of national interest. The 14 patches, which were allowed to interact via a travel matrix, were individual aimags (Bayan-Ölgii, Bulgan, Darkhan-Uul, Dornod, Khovd, Orkhon, Övörkhangai, Selenge, Uvs), combinations of two (Dornogovi + Ömnögovi, Govi-Altai + Zavkhan), three (Arkhangai + Bayankhongor + Khövsgöl) or five aimags (Dundgovi + Govisümber + Khentii + Sükhbaatar + Töv), and the municipality of Ulaanbaatar (Appendix A). Inter-patch mixing was generally only significant between neighbouring patches and between each of the other patches and Ulaanbaatar. The importation of A(H1N1)pdm09-infected cases into border patches was modelled using the time-courses of the 2009 pandemic in neighbouring countries and the relative frequency of border crossings. The basic reproduction rate ($R_0$) used as the baseline in the model was based on epidemiological observations in other countries, but a wide range of values, including more severe scenarios with $R_0$ varying around 2, was explored. The data were modelled and graphically displayed using Matlab (MathWorks Inc., Natick, USA).

The model was configured to allow evaluation of the likely effects of travel restrictions, school closure, generalized social distancing, quarantining of close contacts of presenting cases and distri-
bution of an antiviral drug to the ill and their close contacts.

Assessment of intervention strategies

Pandemic scenarios beginning at week 35 were simulated. The impact of travel restrictions, school closure and generalized social distancing was assessed, with each intervention beginning at various time points ranging from week 35 to week 49 and varying in duration from 2 to 12 weeks. The effects of the ongoing quarantining of the contacts of presenting cases during the epidemic and of the continuous distribution of an antiviral drug to contacts until the national stockpile of the drug was exhausted were also investigated, with the presumption that each of these interventions would be implemented from the first case. It was conservatively assumed that the cases themselves could not be quarantined early enough to reduce their overall infectiousness.

Latin-hypercube sampling (LHS) was used for a sensitivity analysis of the various parameters describing the effects of intervention timing and efficiency on intervention impact. The LHS technique allowed the average impact of an intervention to be estimated despite uncertainties in the characteristics of the pathogens involved and the nature and intensity of the population mixing. Sampling was conducted over many different parameters related to travel and importation rates, the virus-dependent factors of transmission and the details of each intervention (sampling ranges in Appendix A). The LHS approach allowed us to detect possible associations between model parameters (including those characterizing an intervention measure) and various statistics capturing the severity of the pandemic, as well as to estimate the uncertainty around these associations. By using LHS we hoped to identify the intervention strategies that would be optimal across a range of potential pandemic scenarios in Mongolia.

Results

Epidemic curves for the baseline model are shown for Mongolia as a whole (Fig. 1), along with the corresponding observed data for the 2009–2010 pandemic. Our model was also able to capture the diversity in observed epidemic curves between patches (Appendix A). Patches encompassing urbanized regions (such as Ulaanbaatar) tended to exhibit early, rapidly-peak ing outbreaks, whereas patches containing rural regions (e.g. Selenge) exhibited more prolonged epidemics. Patches encompassing western aimags (such as Uvs) tended to experience relatively late-peak ing epidemics. Several of the patches containing border regions (such as Bulgan and Omnogovi) displayed double-peaked epidemics.

Three key measures of intervention success were evaluated in the model: the total (presenting) ILI attack rate, the peak ILI reporting rate and the time of peak ILI reporting (Fig. 1). The mean attack rates seen in the model when a single non-pharmaceutical or pharmaceutical intervention was included are shown in Fig. 2. When no intervention was included in the moderate-epidemic model, the mean attack rate was 9.7% and the mean peak ILI rate, which was seen at week 44.5, was about 240 cases per 10000. In the severe epidemic scenario, the mean attack rate was about 23%, and the mean peak ILI rate, of 800 cases per 10000, occurred, on average, during week 42.

Non-pharmaceutical interventions

In the model, the apparent efficacy of social distancing interventions rapidly fell once the frequency of reported ILI cases exceeded approximately 20 cases per 10000. At lower ILI reporting rates, representing the early phases of the modelled pandemic, school closures, generalized social distancing or sustained travel restrictions had a substantial mitigating effect. In the actual epidemic of 2009, an ILI reporting rate

Fig. 1. Statistics used to characterize epidemic timing and severity and to assess intervention impact (upper panel), and observed and modelled incidences of influenza-like illness (ILI; lower panel), Mongolia, 2009–2010

Note: The final attack rate, representing the percentage of the total population infected during the epidemic, is given by the shaded area in the upper panel. The data shown in the lower panel cover the period in which A(H1N1)pdm09 was the dominant subtyped virus, with baseline parameters used in the model.
of 20 cases per 10,000 was recorded during week 40 in the border aimags of Khovd, Dornod and Dornogovi. In the model, school closures or generalized social distancing implemented before the ILI reporting rate reached 20 cases per 10,000, resulted in better mitigation than the very early implementation of travel restrictions of limited duration (which left large numbers of susceptible and infected hosts when the restrictions were relaxed). Although more prolonged interventions appeared relatively more effective in the model, the long-term implementation of any intervention in the field may be hampered by falling compliance and/or logistical challenges. Below we focus on the impact of 4-week interventions in the moderate-epidemic scenario, since the interventions used against the 2009 pandemic in Mongolia appear to have been successfully implemented for about 4 weeks.

In the model, a 50% reduction in mean travel frequency, if applied early in the epidemic (i.e. from week 40, as the ILI reporting rates reached 20 cases per 10,000), delayed the pandemic peak by approximately 1.5 weeks if maintained for 4 weeks and by about 1 week if maintained for 2 weeks. Travel restrictions increased the time-scale over which the modelled pandemic occurred by slowing the spatial spread. They also resulted in a reduction in the peak ILI rate, by about 12%, if enforced for 4 weeks. They only reduced the modelled attack rates by less than 0.1%, however, even when travel frequency was reduced by 95% (Fig. 2).

Substantial reductions in the mean attack rate could be seen, nonetheless, when prolonged school closure or generalized social distancing was added to the model. For school closure to be effective, the attack rate in children had to be over double that in adults. If, for example, schools were closed for 4 weeks from week 40, when the attack rate in children was threefold higher than in adults, the model indicates that the overall attack rate would decrease from 9.7% to approximately 8.6% (Fig. 2) and, perhaps more importantly, that the epidemic peak would be delayed by over a week. School closure implemented before week 40 could delay the time to the pandemic peak by as long as 2 weeks. In general, school closure had only a modest impact on the modelled mean peak ILI rate.

On average, the inclusion in the model of social distancing measures that reduced transmission probability by 50% from week 40 reduced the attack rate from 9.7% to 8.6% (Fig. 2), delayed the time to the peak ILI reporting rate by almost 2 weeks and reduced the peak case-load by about 8%.

The model indicated that the impact of the continuous quarantining of a proportion of the individuals identified as contacts of those who present with an ILI could be very substantial. In a scenario in which 50% of known contacts were traced and quarantined, for example, the peak case-load decreased by 25%, the attack rate was reduced by more than 1.5% (Fig. 2) and the time of peak incidence was delayed by around 1 week.

**Targeted antiviral interventions**

Using the model, we considered the treatment, from the first detected case, of a percentage of infected hosts and the timely prophylaxis of a pro-
portion of their contacts, assuming a finite national stockpile of the antiviral drug used (10,000–500,000 doses). In a scenario in which half of the known contacts were traced and given the antiviral drug, such a targeted intervention reduced the mean attack rate by about 2%, delayed the peak case-load by a mean of 2–3 weeks and reduced the peak case-load by approximately 30% (Fig. 2 and Fig. 3). Although the attack rate decreased by a mean of about 1% when the modelled stockpile was increased from 50,000 doses to 500,000, the corresponding range in the expected attack rates was much greater than this mean reduction, which suggests that the specific nature of the epidemic has a larger impact on the outcome of antiviral usage than the stockpile size (Appendix A). Antiviral drug use, as an isolated measure, appeared relatively more effective in the severe pandemic scenario, where the presenting proportion is generally higher than in the moderate pandemic scenario. In both of these scenarios, however, a suite of non-pharmaceutical interventions had a slightly greater average impact on the attack rate and peak ILI incidence than antiviral drug use as a single intervention (Fig. 3).

**Discussion**

Our model was able to capture the gross characteristics of the actual 2009 influenza pandemic in Mongolia, including the variations between aimags. Although elevated ILI activity was first registered in several border aimags (including Dornogovi) at about the same time in 2009, A(H1N1)pdm09 was probably spread into Dornogovi from northern China and Ulaanbaatar (the site of Mongolia’s sole international airport) via high rates of simultaneous importation of the virus. The particularly severe winter of 2009–2010 is suspected to have affected the pandemic in Mongolia. Our neglect of seasonal and other secondary effects, such as age-dependency in immune response and population mixing, and perhaps our failure to consider all the interventions used, limited our ability to fit the modelled data to the detailed shape of the actual epidemic curve seen in the 2009 pandemic (Fig. 1).

In models involving a range of possible nationwide mitigation strategies in moderate- and severe-pandemic scenarios, mean reductions in the attack rate of up to 2%, reductions in the peak ILI reporting rate of up to 25%, and delays to epidemic peak of over a week were observed. The modelled impact of each mitigation measure that was considered varied significantly with the nature, timing and efficacy of the intervention. Although our results indicate that Mongolia’s capacity to curtail a nationwide epidemic similar to the one in 2009 is limited, even modest reductions in epidemic severity may substantially ease the burden on healthcare systems in resource-poor settings such as Mongolia.

The benefits of travel restrictions in curtailing a nationwide epidemic may be limited once the pathogen involved has reached a congested city from which, and to which, there is widespread travel. In Mongolia, for example, travel restrictions would probably have little impact if implemented only after an epidemic had been established in Ulaanbaatar, the country’s pre-eminent cultural and economic centre. The distinct temporal offsets seen between the epidemics in different states or territories during Australia’s A(H1N1) 2009 epidemic are thought largely to reflect the role of several large or capital cities in disseminating the virus to the surrounding sparsely populated regions in this country.22

Although reduced community mixing through school closures and restricted social interaction on a wider scale appears potentially useful, it is difficult to establish the required nature of effective, generalized, social distancing measures. If we assume that the attack rate in children is over twice that in adults, as expected in a pandemic scenario since children mix sociologically studies indicate that up to half of a person’s daily contacts can typically be named by that person,23 it may also often be possible to trace and quarantine sufficient case contacts to substantially reduce epidemic severity. The tracing of contacts of the very early cases, which usually occur before the threat of a pandemic has been realized, is, however, often difficult. One limitation of this study is that no allowance was made for virus transmission at the household level, which may be boosted when social distancing measures and quarantining are implemented. The apparent benefits of such measures may therefore have been somewhat overestimated.
The widespread prophylactic use of antiviral drugs has more mitigation potential than case treatment alone.\textsuperscript{12,24} Diagnostic and delivery capabilities are, however, crucial in determining the effectiveness of an antiviral campaign. The effectiveness of prophylaxis early in an epidemic is limited by the capacity to distinguish seasonal and epidemic/pandemic IIA cases, which typically requires expensive high-sensitivity diagnostic testing based on polymerase chain reactions. Even without considering this limitation, the present modelling indicates that the timely implementation of a combination of non-pharmaceutical interventions would be at least as effective as the distribution of an antiviral drug. Given that even developed countries struggled to use antiviral drugs to achieve a significant mitigating impact on pandemic influenza in 2009,\textsuperscript{25} the use of non-pharmaceutical interventions – instead of, or in combination with, antiviral distribution – is to be encouraged, especially in resource-poor settings.

Timeliness is key to the success of any within-country intervention strategy. Effective intervention measures need to be triggered by early case detection provided by nationwide surveillance systems with regular case reporting. Monitoring cases in areas containing border crossings, such as Dornogovi, or international travel hubs, such as Ulaanbaatar, is crucial. Containment in regions contributing significantly to border crossings, together with the routine international sharing of surveillance data as recommended by WHO,\textsuperscript{2} should also enhance within-country mitigation capabilities.

The model used in this study was tailored to the ecology of Mongolia during the 2009 pandemic. Climatic, demographic and infrastructural conditions will influence population distribution, mixing characteristics and inter-provincial travel. For example, the higher propensity to travel in summer owing to the traditional nomadic lifestyle of many Mongolians may result in more rapid spatial spread for an out-of-season influenza epidemic than for the pandemic in the winter of 2009–2010. Infrastructural evolution driven by the mining boom – such as the new rail and road networks linking Mongolia with the Russian Federation and border areas of China – may also alter the characteristic mixing between provinces and population clustering. Pandemic planning policy, even in a given country, needs to be regularly reassessed to ensure that it is relevant to the current sociosbehavioural conditions.

Acknowledgements

The authors thank medical personnel in the Mongolian influenza sentinel surveillance sites for collecting morbidity and mortality data and samples for virological examination, and the Centers for Disease Control and Prevention (Atlanta, USA) for the technical and financial support of the National Influenza Centre in Mongolia, through the US/Mongolia Cooperative Agreement (projects U50/CCU024411 and IU51IP000331). The staff of the National Emergency Management Agency kindly provided support during fieldwork in Mongolia in July 2010.

Funding: This paper reports on work commissioned by the Avian and Human Influenza Control, Preparedness and Response Project, National Emergency Management Agency, Mongolia, sponsored by The World Bank. Authors received support from a University of Melbourne McKenzie Fellowship (KJB) and a National Health and Medical Research Council Career Development Award (JM).

Competing interests: None declared.

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Введение

Цель

Учитывая важность гриппа в Монголии, важно оценить предполагаемую эффективность и пользу фармацевтических и нефармацевтических мер по уменьшению распространения вируса гриппа.

Методы

Для оценки влияния различных мер на распространение вируса гриппа в Монголии были использованы математические модели.

Результаты

В рамках моделирования было установлено, что в среднем в несколько месяцев можно снизить интенсивность распространения гриппа на 10–20%.

Заключение

Создание своевременных и эффективных мер по борьбе с гриппом в Монголии может значительно сократить продолжительность и интенсивность пандемии гриппа в этой стране.

Резюме

Преимущества фармацевтических и нефармацевтических мер по борьбе с гриппом в Монголии

В данной статье представлены результаты моделирования, проведенного с целью оценки эффективности различных мер по борьбе с гриппом в Монголии.

Вывод

Математическая модель показала, что своевременное и эффективное применение мер по борьбе с гриппом в Монголии может значительно сократить продолжительность и интенсивность пандемии гриппа в этой стране.

Ключевые слова: грипп, Монголия, фармацевтические и нефармацевтические меры, моделирование, интенсивность распространения.
Resumen

Eficacia posible de las intervenciones farmacéuticas y no farmacéuticas con objeto de mitigar la transmisión del virus de la gripe en Mongolia

Objetivo
Evaluación de la eficacia posible de las intervenciones que están siendo estudiadas para ser aplicadas en Mongolia durante pandemias de gripe futuras.

Métodos
Se construyó un modelo de parche estocástico y compartimental de susceptibilidad, exposición, infección y recuperación para detectar los efectos clave de varias intervenciones (restricciones de viaje, cierre de colegios, distanciamiento social generalizado, cuarentena de contactos cercanos, tratamiento de casos con antivirales y profilaxis de los contactos) sobre la dinámica de las epidemias de gripe. Se evaluó el beneficio posible, así como la coordinación óptima y la duración de cada una de dichas intervenciones por medio de métodos de muestreo para hipercubo latino realizado un cálculo a través de numerosos parámetros posibles de transmisión y mezcla social.

Resultados
Las intervenciones oportunas pudieron reducir de manera considerable la evolución y gravedad de la gripe pandémica en Mongolia. En una hipótesis de pandemia moderada, las medidas tempranas de distanciamiento social disminuyeron la tasa de ataque de aproximadamente el 10% al 7-8%. De igual modo, en una hipótesis de pandemia grave, dichas medidas reducen la tasa media de ataque de aproximadamente el 23% al 21%. En ambas hipótesis de pandemia, tanto moderada como grave, las intervenciones no farmacéuticas demostraron ser tan efectivas como el uso focalizado de antivirales. Las campañas antivirales focalizadas parecieron por lo general más efectivas para las hipótesis de pandemia graves que para las hipótesis moderadas.

Conclusión
Un modelo matemático de transmisión de gripe pandémica en Mongolia indicó que, para que tengan éxito, las intervenciones para prevenir la transmisión deben ponerse en marcha en cuanto se detecten los primeros casos en regiones fronterizas. Las medidas de distanciamiento social podrían tener un impacto de mitigación notable si se introducen en esta fase y se aplican durante varias semanas. En las regiones de ingresos bajos como Mongolia, el distanciamiento social podría ser más eficaz que el uso de antivirales a gran escala.

References

An analysis of the likely effectiveness of pharmaceutical and non-pharmaceutical interventions for mitigating influenza transmission in Mongolia: Appendix A


A1 Dynamical model for pandemic influenza transmission

Below we present the model we use to describe the spread of pandemic influenza in Mongolia, including details of model calibration using A(H1N1)2009 pandemic reporting data. Full source code is available from the authors upon request.

A1.1 SEAIR model for within patch transmission

Within regions that can be considered well connected, we model influenza transmission using a stochastic computational model in which hosts are assumed to mix homogeneously and are classified as being either Susceptible ($S$), Exposed ($E_{np}$, $E_p$), Infectious and presenting for medical attention ($I_{npt}$, $I_{npt}$, $I_p$), infectious but not presenting ($A_{np}$, $A_p$) or Recovered ($RI_{np}$, $RI_p$, $RA_{np}$, $R_p$) (SEAIR). We also track the proportion of hosts who have had recent contact with an infected individual ($C_{np}$, $C_p$). Note that the subscripts $p$, $np$ refer to hosts who have/haven’t received prophylaxis, and $t$ refers to hosts who have received treatment. The equations describing the dynamics may be written:
\[
\frac{dS}{dt} = -(\lambda_p + \lambda_{np}) \frac{S}{N} - x \exp \frac{S}{N},
\]
\[
\frac{dE_p}{dt} = \lambda_p \frac{S}{N} - \gamma E_p - x \exp \frac{E_p}{N},
\]
\[
\frac{dE_{np}}{dt} = \lambda_{np} \frac{S}{N} - \gamma E_{np} - x \exp \frac{E_{np}}{N},
\]
\[
\frac{dI_p}{dt} = \alpha \gamma E_p - \omega I_p - x \exp \frac{I_p}{N},
\]
\[
\frac{dI_{np}}{dt} = \alpha \gamma \psi E_{np} - \omega I_{np} - x \exp \frac{I_{np}}{N},
\]
\[
\frac{dI_{npt}}{dt} = \alpha (1 - \psi) E_{np} - \omega I_{npt} - x \exp \frac{I_{npt}}{N},
\]
\[
\frac{dI_{npt}}{dt} = \alpha (1 - \psi) E_{np} - \omega I_{npt} - x \exp \frac{I_{npt}}{N},
\]
\[
\frac{dA_p}{dt} = \gamma (1 - \alpha) E_p - \omega A_p - x \exp \frac{A_p}{N},
\]
\[
\frac{dA_{np}}{dt} = \gamma (1 - \alpha) E_{np} - \omega A_{np} - x \exp \frac{A_{np}}{N},
\]
\[
\frac{dRI_p}{dt} = \omega I_p - x \exp \frac{RI_p}{N},
\]
\[
\frac{dRI_{np}}{dt} = \omega (I_{npt} + I_{npt}) - x \exp \frac{RI_{np}}{N},
\]
\[
\frac{dRA_p}{dt} = \omega A_p - x \exp \frac{RA_p}{N},
\]
\[
\frac{dRA_{np}}{dt} = \omega A_{np} - x \exp \frac{RA_{np}}{N},
\]

where the force of infection terms are defined as:

\[
\lambda_p = R_{eff} \omega \theta_p (e_i (I_p + A_p) + e_t I_{npt} + I_{npt} + A_{np} + I_{trav}),
\]
\[
\lambda_{np} = R_{eff} \omega \theta_{np} [e_i (I_p + A_p) + e_t I_{npt} + I_{npt} + A_{np} + I_{trav}],
\]
\[
\theta_p = e_s \left( \frac{C_p}{C_p + C_{np}} \right),
\]
\[
\theta_{np} = \left( \frac{C_{np}}{C_p + C_{np}} \right).
\]

Here \( \alpha \) is the proportion of cases that present for medical attention and \( \psi \) is the proportion of these that undergo timely treatment. The parameter \( \omega \) corresponds to the inverse of the infectious period and \( \gamma \) the inverse latent period. The term \( I_{trav} \) is derived from the travel matrix \( M_{trav} \) and corresponds to the additional prevalence in the patch due to travel from all other patches as described in §A1.2. The equations governing the number of contacts who have \( (C_p) \) or have not \( (C_{np}) \) received timely prophylaxis are given by:

\[
\frac{dC_p}{dt} = \kappa \epsilon \gamma \alpha (E_p + E_{np}) - \delta C_p - \lambda_p \theta_p,
\]
\[
\frac{dC_{np}}{dt} = \kappa \gamma [(1 - \epsilon) \alpha + (1 - \alpha)](E_p + E_{np}) + \kappa A_{imp} - \delta C_{np} - \lambda_{np} \theta_{np},
\]

where \( \kappa \) is the contact rate, \( \delta \) is the inverse contact period and \( \epsilon \) is the proportion of contacts that are traced and provided with timely prophylaxis. The parameters \( e_i \) and \( e_t \) denote the anti-viral efficacy against infectiousness following failed
prophylaxis of a contact or following treatment of a presenting case respectively. The term $e_s$ corresponds to the anti-viral efficacy against susceptibility for prophylaxis of contacts. In the absence of any interventions, the effective reproduction number is derived from the basic reproduction number $R_0$ as follows:

$$R_{\text{eff}} = R_0(1 - Z),$$  \hspace{1cm} (A4)

where $Z$ is the proportion of the population with pre-pandemic immunity. We require an additional equation tracking the size of the anti-viral stockpile $O$:

$$\frac{dO}{dt} = -(\kappa \epsilon + \psi) \gamma \alpha (E_p + E_{np}).$$  \hspace{1cm} (A5)

The term $A_{\text{imp}}$ denotes the daily rate of case importation into a given patch. For all but 5 patches $A_{\text{imp}} = 0$, but for those patches with international borders we choose $A_{\text{imp}}$ in order to recover the observed outbreak in a manner that is consistent with the epidemiological data on the 2009 pandemic in neighbouring countries and border crossing statistics. Importations into Dornogovi (via Zamin-Uud on the border with Northern China), Ulaanbaatar (via the country’s sole international airport) and Omnogovi (also bordering with Northern China) are assumed to all have a similar time-dependence, with the importation rate peaking at Weeks 45 and 46 and returning to initial/baseline rates at Week 61. The peak importation rates reflect the frequency of incoming travellers, with the peak importation rate into Dornogovi a third of that into Ulaanbaatar and the peak importation rate into Omnogovi a factor of 10 lower again. Importations into Khovd and Dornod are assumed to occur at a (low-level) fixed rate of 1 and 2 persons per day respectively. Note that we assume imported cases are not undergoing treatment or receiving prophylaxis. In order to conserve the population size of each patch, hosts are removed at an equivalent rate $x_{\text{exp}} = A_{\text{imp}}$ from each state in proportion to state prevalence.

The set of 15 coupled differential equations specified in equations (A1), (A3) and (A5) are solved stochastically using a fixed time step. This transmission model - without the importation and travel terms - has the same structure as the models presented in detail by the authors in McCaw & McVernon (2007) (with the addition of a class of undetected infected hosts) and McVernon et al. (2010). Note that there are subtle changes in nomenclature compared with previous work.

### A1.2 Patch model for spatial transmission

In order to capture the spread of an infectious agent across Mongolia we construct a network patch model in which the entire country is divided into distinct patches. We single out 14 abutting regions which include urbanised regions, regions containing border crossings, sentinel surveillance sites, and other regions of strategic interest, to behave as patches (see Figure A1). This geographical population division allows us to account for diversity in mixing characteristics, propensity for inter-patch travel, the intensity of ILI surveillance and the likelihood of external importation of disease in our model. All patches are chosen to consist of either a single Aimag or a collection of adjoining Aimags, permitting optimal use of the weekly surveillance reports of the number of people presenting with ILI symptoms (collected by the National Centre of Communicable Disease, part of Ministry of Health Mongolia and reported at www.flu.mn) to calibrate a baseline model for the spread of influenza in Mongolia.

The interaction between patches is captured using a mixing matrix. We use the existing national travel statistics as plausibility bounds for the strength of interaction between each pair of patches, but calibrate the inter-patch interaction terms to match the observed outbreak in 2009. With the exception of Ulaanbaatar, each patch is influenced only by its neighbouring patches and Ulaanbaatar. Ulaanbaatar, which acts as the main centre, is linked to all other patches. The baseline travel matrix ($M_{\text{trav}}$) is replicated in Table A1. We calculate the increase in the force of infection due to travel for each patch by summing (over all other patches) the product of the interaction element $M_{\text{trav}}$, the total infectiousness of the presenting and undetected cases in the patch and the inverse of the patch’s population size. Variations in the travel matrix are explored within the LHS framework as described in Table A3.

### A1.3 Model validation

To tune the spatial transmission model to capture the key features of the A(H1N1)2009 pandemic, many of the infection and mixing parameters were varied about initial estimates (made based on previous modelling experience, examination
of available data and anecdotal evidence), resulting in a baseline model with $R_0 = 1.6$, infectious period $(1/\omega)$ of 1.5 days, presenting proportion $(\alpha)$ of 33 per cent, and contact rate $(\kappa)$ of 30 per person per day (in line with upper estimates of contact rates across Europe, Mossong et al. (2008)). In addition several heterogeneities in the population mixing were required to capture key features of the data:

- Patches in which the epidemic exhibited two waves were modelled by subdividing the patch into two (weakly interacting) sub-patches with population sizes proportional to the final attack rate for each wave. Allowing infection(s) to occur in the second sub-patch upon completion of the epidemic in the first reproduces the data well, suggesting the effect is consistent with heterogeneous mixing.

- The presenting proportion in Category II and III surveillance Aimagas was reduced to 15 per cent from the 33 per cent for Category I surveillance areas, in line with the observed reduction in total ILI reporting rate in the lower level surveillance areas.

- The daily number of contacts (per person) in rural patches was reduced to 20 per person per day, two thirds that assumed for urbanised patches.

- The infectious period was assumed to be longer in the remote Aimagas of Khovd, Dornod and Omnogovi (see Table A2) where the duration of time between contact events is likely greater.

The resulting epidemic curves, for the baseline model parameters, are shown for each patch in Figure A2. Figure A3 compares the observed statistics from the ILI data collected in 2009-10 with the corresponding baseline model epidemic statistics for each patch.

### A2 Modelling and assessing intervention strategies

We model the impact of various non-pharmaceutical and pharmaceutical intervention measures as described in §A2.1. In §A2.2 we note the parameter sampling used to explore the average expected impact of an intervention on pandemic severity.

#### A2.1 Modelling interventions

We model the effect of the following intervention measures on the epidemic dynamics:

<table>
<thead>
<tr>
<th>Patch</th>
<th>Ulb</th>
<th>Darkhanul</th>
<th>Orkan</th>
<th>Khovd</th>
<th>Dornogovi</th>
<th>Dornod</th>
<th>Omnogovi</th>
<th>Uvs</th>
<th>Bulgan</th>
<th>Selenge</th>
<th>Overkhangai</th>
<th>West</th>
<th>Khangai</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulb</td>
<td>-</td>
<td>2000</td>
<td>2000</td>
<td>500</td>
<td>2000</td>
<td>500</td>
<td>500</td>
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<td>1000</td>
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<td>1000</td>
<td>1000</td>
<td>15000</td>
</tr>
<tr>
<td>Darkhanul</td>
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<td>0</td>
<td>0</td>
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<td>1000</td>
<td>0</td>
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<td>1000</td>
<td></td>
</tr>
<tr>
<td>Orkan</td>
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<td>1000</td>
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<tr>
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<td>0</td>
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<td>500</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Overkhangai</td>
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<td>0</td>
<td>0</td>
<td>500</td>
<td>0</td>
<td>0</td>
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<td>2000</td>
<td>0</td>
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<td>-</td>
<td>5000</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Khangai</td>
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<td>1000</td>
<td>0</td>
<td>0</td>
<td>1000</td>
<td>0</td>
<td>1000</td>
<td>0</td>
<td>1000</td>
<td>2000</td>
<td>5000</td>
<td>-</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>15000</td>
<td>1000</td>
<td>1000</td>
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<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>2000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table A1: Baseline travel matrix ($M_{trav}$) characterising pair-wise interaction between each of the 14 patches.
• **Travel restrictions**: implemented as a (uniform) reduction of the terms in $M_{\text{trav}}$ by a factor $f_{\text{trav}}$. Given the limited available travel statistics data it is uncertain to what degree travel might be reduced. We thus explore a range of effects, allowing the relative propensity to travel to be reduced by as much as 95 per cent.

• **School closure**: implemented as an overall decrease in the effective reproduction number by a factor $f_{\text{SC}}$. The value of $f_{\text{SC}}$ is determined from the relative attack rate in adults divided by that in children ($AR_A/AR_C$) at the time of intervention as in Glass & Barnes (2007). We allow $AR_A/AR_C$ to vary from 0.3 up to 1, with values at the lower end of this range consistent with observations of the pandemic experience in 2009 in other countries (e.g. McBryde et al., 2009).

• **Generalised social distancing**: implemented as an overall decrease in $R_{\text{eff}}$ by a factor $f_{\text{SD}}$. The impact of social distancing measures such as the closure of public events, restaurants and shops on overall transmission is uncertain, and we explore scenarios in which overall transmission is reduced by up to 50 per cent.

• **Quarantining of close contacts**: implemented using the contact class by setting $\psi = 0$ (i.e. no treatment) and $e_s = 1$ (equivalent to assuming no reduction in susceptibility following quarantine, motivated by fact that by definition quarantined hosts have already been exposed). When using the contact class to model quarantine interventions, we rename $e_i$ as $e_Q$ (the relative impact of quarantining on infectiousness of close contacts) and $\epsilon$ as $\epsilon_Q$ (the proportion of close contacts placed under home quarantine). The impact of quarantining is potentially very strong (depending on the importance of household effects) but uncertain and we thus consider values of $e_Q$ between 0.5 and 1. Note that we conservatively assume that quarantining of cases is not able to be achieved early enough to significantly reduce their overall infectiousness ($e_t = 1$).

• **Distribution of anti-viral courses for treatment of presenting cases and prophylaxis of their traceable close contacts**: implemented using the contact class and varying all 4 relevant parameters $\psi, e_i, e_t$ and $e_s$. We assume that the proportion treated $\psi$ may range from 5 to 50 per cent. The ranges we assign to the anti-viral efficacy parameters are consistent with existing results on the efficacy of oseltamivir (Aoki et al., 2003; Hayden et al., 1999, 2004; Moscona, 2005; Welliver et al., 2001) and include the possibility that the drugs have no effect on transmission. We adopt conservative estimates of the mean efficacy; $e_i = 0.8, e_t = 0.9$, and $e_s = 0.6$.

Note that both quarantining of close contacts and AV distribution each require use of the contact class and thus we cannot consider co-implementation of these measures.

### A2.2 Model parameters for LHS sampling

Below we describe the parameter sampling used to explore a variety of moderate and severe pandemic scenarios and the impact of interventions with varying characteristics.

Note that when we consider the effect of the implementation of multiple intervention strategies, the duration and start date of each are sampled independently.

### A3 Further results

In Figure A4 we show the impact of an isolated anti-viral intervention on the attack-rate (left panel) and peak ILI reporting rate (right panel) as a function of anti-viral stockpile size for a suite of moderate (upper) and severe (lower) pandemic scenarios. The continuous black line corresponds to the fraction of simulations (within each stockpile size bin) for which the stockpile expires, as measured on the right hand vertical axis. The modest dependence of pandemic severity on the available stockpile size is notable. We also note that even in a severe pandemic scenario large anti-viral stockpiles are not necessarily depleted.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean(range)</th>
<th>Sampling (LHS)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_0$</td>
<td>1.6(1.3-1.9)</td>
<td>centrally distributed</td>
<td>Basic reproduction number (severe scenario)</td>
</tr>
<tr>
<td></td>
<td>2.0(1.6-2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Z$</td>
<td>20%(8%-32%)</td>
<td>centrally distributed</td>
<td>Proportion of population with pre-pandemic protection</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>$1/1.0$ days$^{-1}$($1/1.7$ days$^{-1}$-$1/0.7$ days$^{-1}$)</td>
<td>centrally distributed</td>
<td>Inverse latent period</td>
</tr>
<tr>
<td>$\omega$</td>
<td>$1/1.5$ days$^{-1}$($1/2.5$ days$^{-1}$-$1/1.0$ days$^{-1}$)</td>
<td>centrally distributed</td>
<td>Inverse infectious period (Khovd, Dornod, Omnogovi)</td>
</tr>
<tr>
<td></td>
<td>$1/2.5$ days$^{-1}$($1/4.0$ days$^{-1}$-$1/1.8$ days$^{-1}$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\delta$</td>
<td>$1/3.0$ days$^{-1}$</td>
<td>fixed</td>
<td>Inverse contact period</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>33% (13%−53%)</td>
<td>mildly right skewed</td>
<td>Proportion of presenting cases (Category I Sentinel Aimags) (severe scenario)</td>
</tr>
<tr>
<td></td>
<td>50%(20%-70%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\alpha_{rel}$</td>
<td>0.45(0.27-0.64)</td>
<td>centrally distributed</td>
<td>Scaling factor on $\alpha$ for Category II &amp; III Sentinel Aimags</td>
</tr>
</tbody>
</table>

Table A2: Model infection parameters, their mean values and ranges as used in LHS. Note that in a severe pandemic scenario we consider larger values of both $R_0$ and $\alpha$.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean(range)</th>
<th>Sampling (LHS)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
<td>2,375,800</td>
<td>fixed</td>
<td>Total population of Mongolia (individual patch populations)</td>
</tr>
<tr>
<td></td>
<td>58,300 − 1,112,300</td>
<td>fixed</td>
<td></td>
</tr>
<tr>
<td>$\kappa$</td>
<td>30</td>
<td>fixed</td>
<td>Average number of contacts of each infectious case (urban) (rural)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>fixed</td>
<td></td>
</tr>
<tr>
<td>$M_{trav}$</td>
<td>Individual elements are between 0 and 15,000 as shown in Table A1 and we independently sample each element over a range approximately one order of magnitude either side of the mean value.</td>
<td>left skewed</td>
<td>Travel matrix</td>
</tr>
<tr>
<td>$A_{import}$</td>
<td>Time-dependent importation rate introduced for 5 of the 14 patches, ranging from &lt; 1 person per up to a maximum of 14 persons per day during Weeks 45 and 46.</td>
<td>fixed</td>
<td>Rate of importation of infected hosts through border crossings in Dornogovi, Ulaanbaatar, Omnogovi, Khovd and Dornod.</td>
</tr>
</tbody>
</table>

Table A3: Population dependent model parameters, mean values, distributions and ranges as used in LHS.
Figure A1: a) Observed spatial spread of A(H1N1)2009 in Mongolia. Weekly reporting rate by aimag in week 40 (upper panel), 42 (middle panel), 45 (lower panel) of 2009. The shading in each map denotes the ILI reporting rate per 10,000 cases as indicated in the legends. Note that colours represent different reporting rates in different weeks. The black dots indicate confirmed A(H1N1)2009 cases. b) Definitions of patches used in network patch model.
Figure A2: Model epidemic for each patch, as defined in Figure A1, using baseline model parameters.
Figure A3: Patch by patch epidemic statistics (ILI attack rate, peak ILI incidence per 10,000, time of peak ILI incidence, time of ILI reporting rate first exceeding 50 per 10,000, time of ILI reporting first dropping below 50 per 10,000 and duration of ILI incidence above 50 per 10,000) plotted against observed statistics for the 2009 A(H1N1)2009 pandemic. Note that where a patch experienced two waves, the modelled and observed statistics are plotted independently for each wave, and the far right data point in each panel corresponds to the statistics for the national epidemic.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean(range)</th>
<th>Sampling (LHS)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$O$</td>
<td>(10,000-500,000)</td>
<td>uniformly sampled</td>
<td>Anti-viral stockpile size (drug courses)</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>0.2(0.05-0.5)</td>
<td>mildly left skewed</td>
<td>Proportion of contacts of identified cases that are traced and provided with timely anti-virals as prophylaxis</td>
</tr>
<tr>
<td>$\psi$</td>
<td>0.2(0.05-0.5)</td>
<td>mildly left skewed</td>
<td>Proportion of identified cases that are provided with timely antiviral treatment</td>
</tr>
<tr>
<td>$e_s$</td>
<td>0.6(0.45-1.0)</td>
<td>left skewed</td>
<td>Anti-viral efficacy against susceptibility (prophylaxis of contacts)</td>
</tr>
<tr>
<td>$e_t$</td>
<td>0.8(0.65-1.0)</td>
<td>right skewed</td>
<td>Anti-viral efficacy against infectiousness (breakthrough infection in a contact following failed prophylaxis)</td>
</tr>
<tr>
<td>$e_t$</td>
<td>0.9(0.72-1.0)</td>
<td>right skewed</td>
<td>Anti-viral efficacy against infectiousness (treatment of cases)</td>
</tr>
<tr>
<td>$f_{trav}$</td>
<td>(0.05-1.0)</td>
<td>uniformly sampled</td>
<td>Relative propensity to travel when travel restrictions are in place</td>
</tr>
<tr>
<td>$AR_A/AR_C$</td>
<td>(0.3-1.0)</td>
<td>uniformly sampled</td>
<td>Relative attack rate in adults compared to children, which determines $f_{SC}$ as in Glass &amp; Barnes (2007).</td>
</tr>
<tr>
<td>$f_{SD}$</td>
<td>(0.5-1.0)</td>
<td>uniformly sampled</td>
<td>Proportional reduction in transmission due to the implementation of generalised social distancing</td>
</tr>
<tr>
<td>$\epsilon_Q$</td>
<td>(0.0-1.0)</td>
<td>uniformly sampled</td>
<td>Proportion of identified cases that are quarantined</td>
</tr>
<tr>
<td>$e_Q$</td>
<td>(0.5-1.0)</td>
<td>uniformly sampled</td>
<td>Efficacy of quarantine in reducing infectiousness of quarantined cases</td>
</tr>
<tr>
<td>Intervention start date</td>
<td>(Week 39-Week 50)</td>
<td>uniformly sampled</td>
<td>Interventions begin at the start of this week following first importation in Week 35</td>
</tr>
<tr>
<td>Duration of intervention</td>
<td>(2 weeks-12 weeks)</td>
<td>uniformly sampled</td>
<td>Duration of travel restriction, social distancing and school closure interventions</td>
</tr>
</tbody>
</table>

Table A4: Intervention specific model parameters, their mean values and ranges as used in LHS.
Figure A4: National attack rate (left) and peak ILI incidence (right) and AV stockpile depletion frequencies for a suite of moderate (upper panels) and severe (lower panels) pandemic scenario: the red plot indicates the median result, with the box-plot indicating the 25th and 75th percentiles. Results are binned according to the anti-viral stockpile size ($O$) as calibrated by the horizontal axis. The black line shows the proportion of runs for which the stockpile was depleted at the end of the epidemic, as calibrated by the right-hand vertical axis.
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