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Strategies for containing an emerging influenza pandemic in SE Asia.

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Highly pathogenic H5N1 influenza A viruses are now endemic in avian populations in Southeast (SE) Asia, and human cases continue to accumulate. While currently incapable of sustained human-to-human transmission, H5N1 represents a serious pandemic threat due to the risk of a mutation or reassortment generating a virus with increased transmissibility. Identifying public health interventions which may be capable of halting a pandemic in its earliest stages is therefore a priority. Here we use a simulation model of influenza transmission in SE Asia to evaluate the potential effectiveness of targeted mass prophylactic use of antiviral drugs as a containment strategy. Other interventions aimed at reducing population contact rates are also examined as reinforcements to an antiviral-based containment policy. We demonstrate that elimination of a nascent pandemic may be feasible using a combination of geographically targeted prophylaxis and social distancing measures if the basic reproduction number of the novel virus is below 1.8. We predict that a 3 million course stockpile should be sufficient for elimination. Policy effectiveness critically depends on the ascertainment rate of clinical cases and the speed with which antiviral drugs can be distributed.

The continuing spread of the H5N1 highly pathogenic avian influenza (HPAI) in wild and domestic poultry in SE Asia represents the most serious human pandemic influenza risk for decades^{1,2}. Great potential benefits would be gained from any intervention capable of containing the spread of a pandemic strain and eliminating it from the human population. However, the rapid rate of spread of influenza – as witnessed both in annual epidemics and past pandemics³⁻⁵ – poses a significant challenge to the design of a realistic control strategy.

The basic reproduction number⁶, R_0 , quantifies the transmissibility of any pathogen, being defined as the average number of secondary cases generated by a typical primary case in an entirely susceptible population. If $R_0 > 1$ a disease can spread, while if $R_0 < 1$, chains of transmission will inevitably die out. Hence the goal of control policies is to reduce R_0 to below 1, by eliminating a proportion $1 - 1/R_0$ of transmission. This can be achieved in three ways: (a) by reducing contact rates in the population (through ‘social distance measures’); (b)

by reducing the infectiousness of infected individuals (through treatment or isolation); or (c) by reducing the susceptibility of uninfected individuals (by vaccination or antiviral prophylaxis).

Vaccination and antiviral drugs offer protection against infection and clinical disease. However while effective vaccines exist for interpandemic flu, candidate H5N1 vaccines have unproven effectiveness⁷ and production delays would in any case limit availability in the first months of a pandemic. Antiviral agents – and in particular the neuraminidase inhibitors, which show experimental effectiveness against all influenza A subtypes^{8,9} – are therefore a key plank of recently revised pandemic preparedness plans in several countries¹⁰.

For antivirals to significantly reduce transmission, prophylactic use is necessary. Large-scale prophylaxis has the potential to limit spread substantially in a developed country context¹¹, but the very large stocks of drug necessary make this policy impractical if the pandemic is already global. However, might such a policy nonetheless be a feasible strategy if applied at the source of a new pandemic, when repeated human-to-human transmission is first observed? We address this question here, focusing on identification of the threshold level of transmissibility below which containment of any new pandemic strain might be feasible.

Modelling pandemic spread

We model spread in SE Asia, as that region remains the focus of the ongoing avian H5N1 epidemic and is where most human cases have occurred. Greater data availability led us to model Thailand, not a perceived greater risk of emergence compared with other countries in the region; we believe our conclusions are also valid for other parts of SE Asia.

We constructed a spatially-explicit simulation of the 85 million people residing within Thailand and in a 100km zone of contiguous neighbouring countries. The model explicitly incorporates households, schools and workplaces as these are known to be the primary contexts of influenza transmission¹²⁻¹⁴(see Fig1 and Methods) and because control measures

can readily target these locations. Random contacts in the community associated with day-to-day movement and travel are also modelled..

Natural history and transmission parameters

Fundamental to the feasibility of any containment strategy is the transmissibility of the emergent virus, as quantified by R_0 . Reliable past estimates of transmissibility are rare, perhaps due to the antigenic diversity of the influenza and consequent complex impact of population immunity on transmission.

We reanalysed incubation period and household transmission data (see Methods) and derived new natural history parameters which predict a profile of infectiousness through time which is remarkably consistent with viral shedding data from experimental infection studies (see Figure 1g¹⁵). This profile gives an estimate of the serial interval or generation time, T_g (the average interval from infection of one individual to when their contacts are infected), of 2.6 days – to be compared with the value of ~4 days assumed by most past modelling¹⁶. Reanalysis of both US and UK 1918 mortality data using this new value of T_g revises pandemic influenza R_0 estimates⁵ downwards to approximately 1.8 (Figure 1a) – yielding a predicted infection attack rate during a pandemic of 50-60%, consistent with what was seen in the 1st and 2nd waves of past pandemics (see Figure 2b). A value of 1.8 is also consistent with annual interpandemic attack rates seen for households where all members were highly susceptible to the prevalent strain¹⁷ (see Supplementary Information). We additionally assume that 50% of infections result in clinically recognisable symptoms, with the other 50% being too mild to be diagnosed clinically¹⁸.

It is not certain that these parameter estimates would be applicable to any new pandemic strain. It is possible that the mutations or reassortment event that give rise to the new viral strain might initially only increase its transmissibility a little over the $R_0=1$ threshold for self-sustaining transmission. In that case, additional mutations would need to accumulate for viral fitness to increase to its maximum. Given the extended viral shedding (and symptomatic

disease) seen in severe human cases of avian H5N1 infection, this also might mean that the T_g of the initial pandemic strain could be considerably greater than for currently circulating human influenza viruses. We therefore examine the ability of control measures to contain pandemic spread not just at a single value of R_0 , but for different values in the range $1 < R_0 < 2$, and analyse model sensitivity to the assumed value of T_g .

Baseline epidemic dynamics.

We consider the scenario that a novel transmissible ($R_0 > 1$) pandemic strain arises as a result of mutations or a reassortment event in a single individual infected with an avian virus. We seed simulations with a single infection in the most rural (i.e. lowest population density) third of the population, assuming rural populations are most likely to be exposed to the avian virus. Figure 2 shows the typical pattern of spread for an emergent pandemic initiated by such a seeding event assuming $R_0 = 1.5$ – though note that for low R_0 most epidemics seeded by a single individual go extinct by chance before becoming established in the population.

The pattern of spatial spread (Figure 2a and Supplementary Information video 1) is of interest: for the first 30 days, cases tend to be limited to the region around the seeding location, with few ‘sparks’ outside that area. However, as case numbers increase exponentially, so does the frequency with which infection events span large distances, and the epidemic rapidly transforms from being predominantly local to country-wide between day 60 and 90. Any containment policy needs to be effective before this transition – in part because logistic constraints are likely to preclude containment of a widely disseminated epidemic, but also because the probability of international export of infection becomes high once case numbers reach the thousands¹⁹.

For $R_0 = 1.5$, the epidemic in the modelled population of 85 million peaks around day 150, and is largely over by day 200, at which point 33% of the population have been infected. At $R_0 = 1.8$ the epidemic peaks around day 100 and infects around 50% of the population.

Impact of antiviral prophylaxis

In containment strategies, we focus on 2 principal outcome measures: (a) the probability of preventing a large outbreak (which would eventually lead to a global pandemic); (b) the number of courses of drug (here assumed to be oseltamivir) required to achieve containment.

Blanket prophylaxis of an entire country or region should be able to eliminate a pandemic virus with an R_0 of 3.6 or greater (see Methods). However, such a policy would require enough drug to prophylax everyone for up to 3 weeks (i.e. at least 2 courses per person), and hence is unfeasible. Targeted strategies are therefore needed which minimise drug usage while maximising impact.

Social targeting is the most straightforward approach – namely prophylaxing individuals in the same household, school or workplace as a newly diagnosed symptomatic case.

Unfortunately, if such a policy is only initiated after 20 or more cases, purely social targeting only has a $\geq 90\%$ probability of eliminating the pandemic strain if $R_0 \leq 1.25$ (lowest curve of Figure 3a; see also Supplementary Information). In reality, at least 10 cases might need to be detected to be sure that viral transmissibility had significantly increased²⁰, and detection and decision-making delays could easily mean 20-30 cases had arisen before policy initiation. A containment policy will therefore probably need to go beyond social targeting to succeed. Since most community contacts are local, geographic targeting – namely when a case is detected, prophylaxing the whole population in neighbourhood of the household of the case – is an obvious policy extension, though one which undoubtedly will dramatically increase the logistical challenges to delivery. In the absence of detailed administrative boundary data, we simulated geographic targeting as the prophylaxis of the population within a ring of a certain radius centred around each detected case, though in reality targeting administrative areas is likely to be more practical. For socially or geographically prophylaxis, we assume individuals are given a single course of 10 days of drug, after which time they come off drug unless more cases have arisen in their vicinity, in which case a second round of prophylaxis is delivered. The policies therefore automatically cease within 10 days of the last case being reported.

Our analysis indicates that the substantial additional effort required to deliver a geographic policy pays substantial dividends in policy effectiveness. With a 2 day delay from case onset to prophylaxis, a 5km ring policy is capable of containing pandemics with an R_0 of 1.5 (Figure 3a) at the cost of an average of 2 million courses (Figure 3b) - though the maximum number of courses needed can be an (unfeasible) order of magnitude for scenarios where cases arise in Bangkok at an early stage of the outbreak. Policy effectiveness increases with the radius of the treatment ring selected (though little benefit is gained from exceeding 10km), but so does the number of courses required (Figure 3b). Policy outcome is still sensitive to the speed of case detection and drug delivery, but containment is always substantially better than for the purely socially targeted policy (Figure 3d).

Since pure radial prophylaxis is costly in terms of drug, we also examined a policy variant which limits the number of people targeted for prophylaxis per case by only targeting the nearest m people (where $m=10,000-50,000$) within 10km of a newly diagnosed case. In areas of low population density, this drug-sparing policy has the impact of a pure 10km policy, but in high density areas many fewer courses of drug are used. The improved effectiveness in rural areas outweighs decreased effectiveness in urban areas resulting in greater impact than a pure 5km policy and much lower drug use (Figure 3e-f).

Epidemiologically, elimination either occurs because the treatment strategy reduces R_0 to below 1, or because it reduces it to close to 1 when the epidemic is small, hence enhancing the probability of random extinction. In scenarios where the pandemic strain is successfully eliminated, geographic spread is usually limited. For example, the root-mean-square (rms) radius of spread is 27km for $R_0=1.5$ using the 5km radial geographic targeting strategy.

When containment is successful, total case numbers are also limited to an average of fewer than 150 cases.

Policies to increase social distance

Measures to increase social distance have been employed in past pandemics, and remain important options for responding to future pandemics¹. Predicting the impact of policies such as closing schools and workplaces is difficult, however, as potentially infectious contacts may be displaced into other settings. Furthermore, it is likely that population contact rates change spontaneously (as well as a result of policy) during severe epidemics (e.g. 1918) in response to the perceived risk. Therefore the estimates of pandemic transmissibility we derive from past pandemics may implicitly incorporate the effects of some degree of social distancing.

We are therefore deliberately conservative in the assumptions made as to the impact of school and workplace closure here, by assuming household and random contact rates increase by 100% and 50% respectively for individuals no longer able to attend school or work. Figure 4a illustrates how adding area-based school and workplace closure, to a drug-sparing prophylaxis policy increases policy effectiveness significantly, with the combined policy having a >90% chance of elimination for $R_0=1.7$.

Quarantine zones – in which movements in and out of the affected area are restricted – are another strategy for enhancing containment, and may in any case be thought necessary to prevent population flight from affected areas or people deliberately entering prophylaxis zones to receive drug. Figure 4a (see also Supplementary Information video 2) shows that such a strategy can dramatically boost the effectiveness (to 90% containment at $R_0=1.8$) of a radial geographic targeted prophylaxis even if only 80% effective at reducing movements. Combining school and workplace closure with area quarantine and prophylaxis further increases policy effectiveness (90% containment at $R_0=1.9$) and as importantly, the robustness of the policy to shortcomings in case identification or treatment rates. For all these policies, containment is typically achieved after fewer than 200 cases have been detected.

Logistical constraints and sensitivity to parameter assumptions

Other constraints may affect the ability of public health authorities to deliver containment policies. Figure 4c shows that size of antiviral stockpile can have a substantial effect on

policies which use pure radial geographic prophylaxis since very large numbers of courses are required to prophylax around cases arising in large urban areas. However policies employing drug-sparing geographically-targeted prophylaxis (Figure 4d) retain high effectiveness so long as at least 3 million drug courses are available. For the scenarios where containment fails given a finite stockpile, Figure 4e shows that even an unsuccessful containment strategy can delay wide-scale spread by a month or more – a potentially critical window of opportunity for accelerating vaccine production.

Another possible constraint is that capacity to implement these containment policies may not be present in all countries in the region, A policy restricted to one country alone may have a substantially reduced chance of success (Figure 4f and Supplementary Information video 3), should the initial case cluster arise in a border region.

Multiple assumptions inevitably need to be made in undertaking preparedness modelling for a future emergent infection. Sensitivity analyses are therefore critical to assessing the robustness of policy conclusions. Here, critical assumptions not already discussed include (a) the ratio of within-place to community transmission, (b) the expected generation time, T_g , of a new pandemic strain (largely determined by the duration of viral shedding and therefore infectiousness), (c) the level of heterogeneity in individual infectiousness (e.g. ‘superspreaders’²¹), (d) antiviral efficacy/take-up, and (e) the sensitivity and specificity of case detection during the control programme. The impact of these assumptions on model output is presented in the Supplementary Information, but in summary, (d) and (e) are – as one might expect – the most critical. If antiviral coverage or efficacy is considerably less than assumed, then policy effectiveness is substantially reduced. Similarly, if surveillance picks up fewer than 40% of infections (i.e. 80% of symptomatic cases), again policy effectiveness is reduced. Poor surveillance specificity (i.e. false positives) has an indirect effect on effectiveness through wasted drug and logistical capacity..

Conclusions

We have shown that containment and elimination of an emergent pandemic strain of influenza at the point of origin is potentially feasible using a combination of antiviral prophylaxis and social distance measures. A key conclusion is the need for multiple approaches: simple socially-targeted prophylaxis is unlikely to be sufficient if the emergent virus has transmissibility near that of past pandemic viruses. Geographically targeted policies are needed to achieve high levels of containment, with area quarantine being particularly effective at further boosting policy effectiveness. The only scenario under which purely socially targeted strategies might be sufficient would be if viral transmissibility evolved incrementally and the emergent virus initially had R_0 only slightly above one (see Supplementary Information); however R_0 will be probably be uncertain at the time containment policies have to be implemented, arguing for policies be precautionary in assuming transmissibility will be comparable with that seen in past pandemics.

A number of key criteria need to be met for a high probability of success: (a) rapid identification of the original case cluster, (b) rapid and sensitive case detection and then delivery of treatment to targeted groups – preferably within 48 hours of a case arising, (c) effective delivery of treatment to a high proportion of the targeted population – preferably >90%, (d) sufficient stockpiles of drug – preferably 3+ million courses of oseltamivir, (e) population cooperation with the containment strategy and, in particular, any social distance measures introduced, (f) international cooperation in policy development, epidemic surveillance, and control strategy implementation. Lastly, containment is unlikely if R_0 exceeds 1.8 for the new pandemic strain. While our analysis of past pandemics suggests that transmissibility will be in this range, it is unlikely that sufficient data will exist to verify this before a containment policy needs to be introduced.

The mathematical model we have used to examine the feasibility of pandemic containment is perhaps the largest-scale detailed epidemic microsimulation yet developed. A key modelling goal was parsimony. While the representation of the population is detailed, this detail is underpinned by available demographic data. The natural history parameters used here have been estimated from primary data on existing influenza strains. The model has 5 key

transmission parameters, of which 2 were estimated from household data and the remaining 3 were qualitatively calibrated to historical age-dependent attack rates. We believe that this type of simulation will increasingly become a standard tool for preparedness planning and modelling of novel disease outbreaks.

Given the set of criteria listed above for successful containment, the obstacles to practical implementation of such a strategy are undoubtedly formidable. Surveillance is perhaps the single greatest challenge. Success depends on early identification of the first cluster of cases caused by the pandemic strain²⁰, and on detection of a high proportion of ongoing cases. Some level of mildly symptomatic infection is to be expected (and has been observed for human H5N1 infections²²), but key to successful containment is the proportion of such cases and their infectiousness. Should the high pathogenicity of recently reported human infections with the H5N1 virus be even partly maintained, then containment might paradoxically be more likely as case-ascertainment levels would be higher.

Achieving the rapid delivery of antiviral drug to a large proportion of the population poses many challenges. Thailand, the country modelled here, is one of the best prepared and equipped countries in the region in being able to implement a large-scale and very rapid public health intervention. Other countries in the region need considerable development input in basic healthcare and disease surveillance infrastructure in order to meet the needs of containment.

Antiviral resistance represents an as yet unquantifiable challenge to a prophylaxis-based containment strategy. Key is not whether genotypic or clinical resistance is seen in a percentage of individuals, but whether resistant viruses are capable of self-sustaining transmission (*i.e.* have $R_0 > 1$). As yet, the evidence is indicative that fitness deficits mean transmissibility is limited for oseltamivir-resistant strains^{23,24} but the possibility that compensatory mutations which increase transmissibility might be selected cannot be ruled out completely. If a transmissible resistant strain did emerge during a containment policy, it would be essential for prophylaxis to cease, lest wild-type virus be eliminated and the world be left with a pandemic of resistant virus. If prophylaxis were abandoned, the likely higher

fitness of wild type would give every chance that the resistant strain would then be excluded from the population.

A feasible strategy for containment of the next pandemic offers the potential of preventing millions of deaths. It is therefore in the interest of all countries to contribute to ensuring the resources, infrastructure and collaborative relationships are in place within the region currently most likely to be the source of a new pandemic. Even if the challenges are great, the costs of failure are potentially so catastrophic that it is imperative for the international community to prepare now to ensure containment is given the best possible chance of success.

Methods

Demographic data: The model used Landscan data²⁵ to generate a simulated population realistically distributed across geographic space (Figure 1a). Thai census data^{26,27} on household size and age distributions was used for demographic parameterisation (Figure 1b,c). Thai National Statistical Office data²⁷ was used to determine the number and proportions of children in school as a function of age, and Thai Dept. of Education²⁸ data on 24,000 schools was used to determine the distribution of school sizes (Figure 1d). Data on travel distances within Thailand was limited; here we used data collected in the 1994 National Migration Survey^{29,30} on distances travelled to work (Figure 1e and see Supplementary Information) to estimate movement kernel parameters. The best fit kernel had asymptotic power law form as a function of distance d given by $f(d) \sim 1/\left[1+(d/a)^b\right]$, where $a=4$ km and $b=3.8$. Thai workplace sizes³¹ also follow a power law distribution³² with an estimated maximum single workplace size of approximately 2300, and a mean of 21.

Disease data: The natural history of any H5 based pandemic strain will not be known until it emerges, so we used parameter estimates for current human influenza subtypes, and employed sensitivity analyses to investigate what impact deviation from these estimates would have on policy effectiveness (see Supplementary Information). The mean and

standard deviation of the incubation period distribution were estimated as 1.48 and 0.47 days respectively from data on a multiple exposure event occurring on an aeroplane³³

We adopt a more biologically realistic approach than most past modelling studies (though see ref. ³⁴), and rather than assuming infectiousness is constant from the end of the latent period to recovery, we model it as a function, $\kappa(T)$ (assumed normalized), depending on the time elapsed from the end of the latent period. The generation time, T_g , is just given by the mean latent period plus $\int_0^\infty T\kappa(T)dT$. Experimental infection data³⁵ indicates the start of symptoms to be coincident with a sharp increase in viral shedding, so we assume infectiousness starts at the end of the incubation period. We further assume a 0.25 day delay from when symptoms start to when diagnosis or health-care seeking behaviour is likely. We employed Bayesian methods (see Supplementary Information) to estimate $\kappa(T)$ from data collected in a recent household study of respiratory disease incidence^{36,37}. Combined with the estimated incubation period distribution, this gives the profile of infectiousness shown in Figure 1f. T_g is estimated as 2.6 days (95% credible interval: 2.1-3.0) – shorter than previously assumed (though see ref. ³⁸).

Transmission model: The model is a stochastic, spatially structured, individual-based discrete time simulation. Individuals are co-located in households, with households being constructed to reflect typical generational structure while matching empirical distributions of age structure and household size for Thailand (Figure 1b,c). Households are randomly distributed in the modelled geographic region with a local density determined by the Landsat data²⁵. In any timestep of $\Delta T = 0.25$ days, a susceptible individual i has probability $1 - \exp[-\lambda_i \Delta T]$ of being infected, where λ_i is the instantaneous infection risk for individual i . Infection risk comes from 3 sources: (a) household, (b) place, and (c) random contacts in the community. The last of these depends on distance and represents random contacts associated with movements and travel, and is the only means by which infection can cross national borders. Analysis of household infection data (see Supplementary Information), gave a within-household R_0 of 0.6 and an overall R_0 of 1.8. We partition non-household transmission to give levels of within-place transmission comparable with household

transmission (i.e. $R_0 \approx 0.6$) and to qualitatively match 1957 pandemic age-specific attack rates. When varying R_0 , the relative proportions of household, place and community transmission were kept fixed. Full model details are given in the Supplementary Information.

Antiviral drug action: We use recent statistically rigorous estimates of antiviral efficacy³⁹, but these are broadly consistent with previous estimates²³. Prophylaxis of uninfected individuals is assumed to reduce susceptibility to infection by 30%, infectiousness if infection occurs by 60%, and the probability of clinically recognisable symptoms by 65%³⁹. In theory therefore, blanket prophylaxis of a population should be able to contain a pandemic with an R_0 of $1/[(1-0.6)(1-0.3)]$, approximately 3.6. Treatment of a symptomatic case is assumed to reduce infectiousness by 60% from when treatment is initiated. Overall, for the parameter values used here, antiviral treatment of a symptomatic case can reduce total infectiousness throughout the course of infection by a maximum of 28%.

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Figure Legends

Figure 1. Data. (a) Modelled population density of Thailand and 100km contiguous zone of neighbouring countries, based on Landscan²⁵ data, plotted on logarithmic scale (light=low density, dark=high density). Inset shows Bangkok in more detail. (b) Age distribution of Thai population in 2003 in 5 year bands and corresponding age distribution of simulated population. (c) as (b) but showing distribution of household sizes. (d) Observed (solid lines) and modelled (dashed lines) distributions of school sizes (blue=elementary, green=secondary, red=mixed). (e) Probability of travelling over a certain distance to work estimated from data and from the simulated population. (f) Weekly excess influenza-related mortality in 1918-19 in GB and corresponding estimates of the reproduction number, R , calculated assuming $T_g=2.6$. (g) Viral shedding data for experimental influenza infection³⁵ compared with the modelled profile of infectiousness over time. Note that the infectiousness profile was not fitted to shedding data. See Methods and Supplementary Information for more details.

Figure 2. Expected pattern of spread of an uncontrolled epidemic. (a) Sequence of snapshots of the epidemic showing extent of spread of a single simulation of a $R_0=1.5$ epidemic. Red indicates presence of infectives, green the density of people who have recovered from infection or died. (b) Daily incidence of infection over time in the absence of controls for $R_0=1.5$. Thick blue line represents average for realisations resulting in a large epidemic, grey shading represents 95% envelope of incidence timeseries. Multiple coloured thin lines show a sample of realisations, illustrating large degree of stochastic variability. (c) Root Mean Square (RMS) distance from seed infective of all individuals infected since the start of the epidemic as a function of time. Thick blue line represents average distance for realisations resulting in a large epidemic, grey shading represents 95% envelope. (d) Proportion of the population infected by age averaged across realisations giving large epidemics, for $R_0=1.5$. The infection attack rate is 33% for $R_0=1.5$, and 50% for $R_0=1.8$. (e) Distribution of number of secondary cases per primary case during the exponential growth phase of a $R_0=1.5$ epidemic. Between 50 and 1000 realisations were used to calculate all averages (see Supplementary information).

Figure 3. Prophylaxis strategies. We assume 90% of clinical cases (=45% of infections) are detected. Social targeting assumes prophylaxis of 90% of household members and 90% of pupils or colleagues in 90% of the schools or workplaces of detected cases. Geographic targeting assumes 90% of people within 5, 10 or 15km of a detected case are also prophylaxed. (a) Probability of eliminating an otherwise large epidemic using social plus geographic targeting, as a function of R_0 of the new strain and the radius of prophylaxis. Results assume policy initiation after 20 cases detected and a 2 day delay from case detection to prophylaxis. Error bars show exact 95% confidence limits. (b) as (a) but showing average numbers of drug courses required for containment of an otherwise large outbreak. (c) Map (of 150x150km square of northern Thailand) showing extent of spread during one contained $R_0=1.8$ epidemic assuming 10k radial prophylaxis and other parameters as (a). Blue represents treated areas. (d) as (a), but varying the delay (from 0-4 days) from case detection to prophylaxis for the 5km radius policy. (e-f) as (a-b) but for drug-sparing policies which target only the nearest 10, 20, 30 or 50 thousand people within 10km of a detected case.

Figure 4. Social distance measures. (a-b) as Fig 3(a-b), but showing impact of drug-sparing prophylaxis (50,000 courses per case, as Fig 3e) combined with: no social distance measures (as Fig 3); closure of 90% of schools and 50% of workplaces within 5km of a detected case for 21 days; 80% 'area quarantine' (i.e. reduction by 80% of travel in and out of a zone defined by merging 5km rings around all detected cases) for 21 days; combination of school/workplace closure and area quarantine. (c) as (a) but showing effect of limiting availability of antiviral drugs to 1, 3 or 5 million courses on the effectiveness of the combined area quarantine and 5km radial prophylaxis policy. (d) as (c) but for drug-sparing geographic prophylaxis (50,000 courses per case) plus area quarantine. (e) Case incidence over time without pandemic control and with the 3 million course policy of (d), showing the

approximate 1 month delay achieved even when containment is unsuccessful ($R_0 = 1.9$). (f) as (a), but showing the reduction in policy effectiveness seen if the combined school/workplace closure and drug-sparing prophylaxis policy is restricted to Thailand alone.







