The impact of surveillance and control on highly pathogenic avian influenza outbreaks in poultry in Dhaka division, Bangladesh

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Abstract

In Bangladesh the poultry industry is an economically and socially important sector, but is persistently threatened by the effects of H5N1 highly pathogenic avian influenza. Thus, identifying the optimal control policy in response to an emerging disease outbreak is a key challenge for policy-makers. To inform this aim, a common approach is to carry out simulation studies comparing plausible strategies, while accounting for known capacity restrictions. In this study we perform simulations of a previously developed H5N1 influenza transmission model framework, fitted to two separate historical outbreaks, to assess specific control objectives related to the burden or duration of H5N1 outbreaks among poultry farms in the Dhaka division in Bangladesh. In particular we explore the optimal implementation of ring culling, ring vaccination and active surveillance measures when presuming disease transmission predominately occurs from premises-to-premises, versus a setting requiring the inclusion of external factors. Additionally, we determine the sensitivity of the management actions under consideration to differing levels of capacity constraints and outbreaks with disparate transmission dynamics. While we find that reactive culling and vaccination control policies should pay close attention to these factors to ensure intervention targeting is optimised, targeted proactive active surveillance schemes appear to significantly outperform reactive surveillance procedures in all instances. Our findings may advise the type of control measure, plus its severity, that should be applied in the event of a re-emergent outbreak of H5N1 amongst poultry in the Dhaka division of Bangladesh.

Introduction

Influenza is a respiratory infection of mammals and birds caused by an RNA virus in the family of Orthomyxoviridae [1]. It incorporates four virus types: types A, B, C, and D. The zoonotic capability of influenza A makes it the most significant of the four types in an epidemiological and public health context, associated with most of the widespread seasonal influenza epidemics and the type capable of causing occasional global pandemics. The natural host of influenza A viruses are an assortment of aquatic bird species. These viruses occasionally spillover into other animal hosts, including domestic poultry, pigs, horses, a variety of carnivores and marine mammals [2]. Sporadically, the viruses adapt to their new animal hosts, leading to enzootic virus circulation for sustained periods. However, apart from a few cases of reputed direct zoonotic transmission of influenza A viruses to humans from wild birds, due to close contact and de-feathering activities [3, 4], humans have been primarily infected with zoonotic influenza viruses via intermediate species to which human exposure is more frequent. Domestic livestock such as pigs and poultry have a key role in this regard. Influenza A is therefore not considered an eradicable disease, with prevention and control the only realistic goals [5].

The prevention and control of Highly Pathogenic Avian Influenza (HPAI) in poultry is of paramount importance, with HPAI viruses causing severe disease in domestic poultry with a high death rate [6]. The specific intervention actions to be taken with regards to regulating marketing, imposing movement restrictions or quarantine measures, culling and vaccinating can vary according to local circumstances and from country to country. There is no one solution for all situations, and a balance must be established among effective, feasible and socially acceptable control measures that safeguard the short-term and long-term livelihoods of farmers and the health of the population.

In general, however, a number of basic measures are common to all circumstances. One such measure is that infected birds and those in contact with them must be humanely and safely culled to halt spread of the disease. This limits spread by decreasing the amount of virus released from any one site. However, usually this alone cannot completely prevent further spread because some virus will have been released before culling commences, and often before the disease is detected. As a result, pre-emptive culling (the culling of animals before they are found to be infected) can be used to attempt to make this a more proactive measure. Use of widespread pre-emptive culling based on defined areas around an outbreak has been a standard implementation of this protocol [7]. In Bangladesh, case detection, identification of premises deemed to be in direct contact with a premises reporting infection, and subsequent stamping out of flocks remain the key platforms of HPAI control programmes [8].

Disease control programs may also aim to create impediments to spread. An essential part of this is to create an environment in which there are relatively few locations that may become easily infected, with vaccination one of the main methods available for achieving such a goal [7]. Vaccination against HPAI aims to reduce levels of virus shed into the environment and stop infection spreading, as well as preventing clinical disease. It has been implemented and encouraged as part of a control program in poultry in parts of Asia, with it being found in Vietnam that within-flock reproductive numbers for premises reporting H5N1 infection were lower in an outbreak period using both depopulation and nationwide systematic vaccination campaigns, compared to an outbreak period employing depopulation control measures alone [9]. Recent positive developments have seen vaccines against H5N1 and H7N9 prevent birds from shedding the virus through their mouths and droppings, thus stopping transmission from one bird to another [10]. Of particular importance is ensuring the vaccines used have high efficacy. In Bangladesh, although vaccines against HPAI have been available since 2012 for use on commercial layer and breeder farms (M.G. Osmani and M.A. Kalam, personal communication), a recent H5N1 surveillance study found no significant difference in anti-H5 seropositivity between vaccinated and unvaccinated chickens, indicating a failure of the vaccination program and a need for updated poultry vaccines [11].

Naturally, policy effectiveness will depend critically on how swiftly clinical cases are diagnosed and the speed with which the chosen control measure can be administered. By employing active surveillance of premises (i.e. activities which are frequent, intensive and aim at establishing the presence or absence of a specific disease) the time for identifying cases and notifying an infected flock may reduce.

Although active surveillance activities can be expensive and time-consuming, there are notable examples of the benefits of strengthening influenza surveillance programs. Intensification of surveillance has helped control and limit the spread of HPAI viruses among poultry on a national scale (e.g. Nigeria [12]), while early detection of HPAI H5N1 viruses through enhanced surveillance in wild birds and domestic poultry has been a key measure to ensure rapid disease control on a continental scale in the case of the European Union [13]. Improved influenza virus surveillance in pigs revealed that influenza virus transmission from humans to swine is far more frequent than swine-to-human zoonosis [14]. The public availability of genetic sequence data from databases such as GenBank have allowed pioneering studies to come into fruition, setting out to characterise the cross-species nature and the migration of influenza A viruses on a global scale [15]. On top of that, there are probable long-term advantages to be gained from active surveillance to outweigh the costs. In the first instance there are trade benefits, with eventual proof of disease absence allowing the opening-up of hitherto untapped markets. Secondly, for diseases such as rinderpest beginning active surveillance means vaccination could cease, saving sizeable amounts of money that otherwise would have been spent on blanket vaccination campaigns [16].

In this paper we assess these assortment of interventions in mitigating the impact of HPAI H5N1 outbreaks within the poultry industry. We focus upon Bangladesh, one of the most densely populated countries in the world [17] and a country that has suffered from recurrent H5N1 outbreaks in poultry as recently as 2012 [18]. The poultry industry in Bangladesh is going through a period of rapid intensification and this, combined with the already substantial poultry population (1194 birds/km^2) [19], make Bangladesh a prime candidate for being the source of newly emerging influenza strains with pandemic causing potential. This is underlined by the recent emergence of a new genotype of HPAI H5N1 viruses in Bangladesh that are now dominant and represent the current threat to domestic poultry and humans in the region [20]. Therefore, it is vital to assess the impact of interventions intending to curb the burden and/or duration of future outbreaks. This analysis was done via simulations of our H5N1 influenza transmission model that has previously been fitted to outbreak data in the Dhaka division in Bangladesh [21], allowing the optimisation of decision making under uncertainty in a principled way. Specifically, we aimed to ascertain both the required intensity of culling and vaccination measures, and type of active surveillance scheme, to optimise a given control objective. Our three primary focuses were then as follows: (i) analyse variability in this choice if in a setting where transmission is believed to be predominately premises-to-premises, versus the scenario where importations and other external environmental/ecological factors are also considered; (ii) inform decisions regarding intervention prioritisation and implementation when under resource constraints that limit control capacity; (iii) determine the sensitivity of the choice of management action to epidemiological characteristics, by considering outbreaks with disparate transmission dynamics.

Methods

The data

Throughout 2010, the Bangladesh office of the Food and Agriculture Organisation of the United Nations (FAO/UN) undertook a census of all commercial poultry premises, listing 65,451 premises in total, of which 2,187 were live bird markets (LBMs). Each premises was visited once, with the premises location recorded along with the number of the following types of avian livestock present during the visit: layer chickens, broiler chickens, ducks, others (e.g. turkeys, quails). Within the census data there were instances of multiple premises having the same location (i.e. identical latitude and longitude co-ordinates). For these occurrences the avian livestock populations were amalgamated, giving a single population for each category at each location.

Of the non-market locations, 23,412 premises had blank entries for all avian types. It has been confirmed this did correspond to no poultry being present on these premises when the census visit occurred, due to the premises either being between poultry stocks or being temporary closed by the farmer due to an ownership transfer taking place, rather than data entry errors (M.G. Osmani, personal communication). We made a simplifying assumption that at any given time an equivalent proportion of premises would not have any avian livestock at the premises. Therefore, we did not make use of these locations in our analysis. While not discussed here the sensitivity of model outputs to this assumption requires further consideration.

Note that owing to the small number of premises in the Dhaka division recorded as having ducks or other poultry types present, approximately 20 premises only, our model simulations comprised purely those premises recorded as having layer and/or broiler chicken flocks present. This totalled 13,330 premises.

Between 2007 and 2012, there were six epidemic waves of H5N1 among poultry in Bangladesh, resulting in a total of 554 premises with confirmed infection and over 2,500,000 birds being destroyed. In previous work [21], we developed a suite of nested models for the Dhaka division that were fitted to the two largest epidemic waves, wave 2 (September 2007 to May 2008) and wave 5 (January 2011 to May 2011), resulting in a total of 232 and 161 premises becoming infected respectively (see Supporting Information for further epidemiological data details). For premises where there were discrepancies between the flock sizes reported in the poultry case dataset and the 2010 poultry premises census the flock sizes stated within the poultry case data was used.

Mathematical model for H5N1 transmission

In this paper, we utilise our preferred model from [21] and investigate the impact of a range of control and surveillance strategies under epidemiological dynamic, resource capacity and control objective uncertainty. This model is a discrete-time compartmental model where at any given point in time a premises i could be in one of four states, S, I, Rep or C: $i \in S$ implies premises i was susceptible to the disease; $i \in I$ implies premises i was infectious and not yet reported; $i \in Rep$ implies premises i was still infectious, but had been reported; $i \in C$ implies that premises i had been culled. Moreover, we considered an overall poultry population at each premises, with the layer and broiler flock sizes at each premises combined. This is based on a conceptualisation where the individual poultry premises is the epidemiological unit of interest. In other words, all poultry types within a premises become rapidly infected such that the entire premises can be classified as Susceptible (S), Infected (I), Reported (Rep or Culled (C).

The reporting delay, time taken for a premises to transition from state I to Rep, accounts for a premises being infectious before clinical signs of H5N1 infection are observed, which may not be immediate [22], followed by the time taken for premises owners to notify the relevant authorities [8]. While the poultry epidemic was ongoing we assumed a premises was not repopulated once culled.

The force of infection against a susceptible premises i on day t was comprised of two terms: (i) the force of infection generated by an infectious premises j (η_{ij}), (ii) a 'spark' term (ϵ_i) to allow for spontaneous, non-distance dependent infections that were unexplained by the susceptibility, transmissibility and kernel components of the model [23]. This captures factors such as importations from outside the study region and transmission from virus-contaminated environments (i.e. fomites). Further, despite backyard poultry not being explicitly included within these models its contribution to the force of infection could be incorporated into ϵ_i.

As a result, the total force of infection has the following general form:

$$\text{Rate}(i,t) = \left(\sum_{j \in I(t) \cup Rep(t)} \eta_{ij} \right) + \epsilon_{i,M}.$$

We assume a seven day delay from infection to reporting (unless specified otherwise), in line with the results of previous work [21, 24]. The contribution by infected premises j to the force of infection against a susceptible premises i satisfies

$$\eta_{ij} = N_{c,i}^{p_c} \times t_c N_{c,j}^{q_c} \times K(d_{ij}).$$

$N_{c,i}$ is the total number of chickens recorded as being on premises i, t_c measures the individual chicken transmissibility, d_{ij} is the distance between premises i and j in kilometres, and K is the transmission kernel to capture how the relative likelihood of infection varies with distance. The model also incorporated power law exponents on the susceptible population, p_c, and infected population, q_c. These power law exponents allow for a non-linear increase in susceptibility and transmissibility with farm size, that have previously been shown to provide a more accurate prediction of farm-level epidemic dynamics [25].

The transmission kernel K in our model is pareto distributed such that:

$$K(d_{ij}) = \begin{cases} 1 & \text{if } 0 \le d_{ij} < x_{\min}, \\ \left(\frac{x_{\min}}{d_{ij}}\right)^{\alpha+1} & \text{if } x_{\min} \le d_{ij}, \\ 0 & \text{otherwise,} \end{cases}$$

where $x_{\min}$ is the minimum possible value of the function (set to 0.1, corresponding to 100 metres, with all between location distances less than 100 metres taking the 100 metre kernel value) and $\alpha \ge -1$. Values of α close to -1 give a relatively constant kernel over all distances, with $\alpha = -1$ corresponding to transmission risk being independent of distance. As α increases away from -1 localised transmission is favoured, with long-range transmission diminished.

The spark term was the same fixed value for every premises, ϵ, with the total rate of infection against a susceptible premises i on day t satisfying

$$\text{Rate}(i,t) = \left(\sum_{j \in I(t) \cup Rep(t)\, t} \eta_{ij} \right) + \epsilon,$$

The previous model fitting study found the wave 5 division-level model, compared to the wave 2 fitted model, had a stronger preference for short-range transmission, with the flock size of infectious premises also having a more prominent role in the force of infection [21]. This allowed us to explore the sensitivity of the management actions under consideration to epidemics with disparate transmission dynamics.

Poultry control policies of interest

In the event of outbreaks of H5N1, a range of policies may be implemented to reduce the risk of further spread of disease. Here we investigate the relative effect of the implementation of three poultry-targeted policy actions: ring culling, ring vaccination and active surveillance. There are typically restrictions on the resources available for enforcing such interventions, limiting the number of poultry and/or premises that can be targeted on any given day. As a consequence, we imposed daily capacities on the maximum number of poultry and the maximum number of premises targeted by each control action, with three differing levels of severity related to the availability of resources. We note that the resource constraints outlined here may not necessarily be representative of the true restrictions present if administering control measures to tackle H5N1 outbreaks within the Dhaka division. However, by exploring a range of constraints we could establish if the action determined optimal was sensitive upon the daily capacity to carry out control.

In each case a baseline control measure of only culling reported premises was performed, with premises being culled on the same day they were reported if possible (with respect to the resource constraints in place). Note that culling of premises reporting infection was carried out in all subsequent control strategies outlined below.

Ring culling

For this choice of action, in addition to the culling of premises reporting infection, all premises within a specified distance of locations with confirmed infection were marked for culling. The distances evaluated here ranged from 1-10km (in 1km increments). In order to simulate the effect of differing resource constraints within the Dhaka division, we impose the following three conditions, based upon low, medium and high culling capacities:

- **Low**: 20,000 daily bird limit, 20 premises limit.
- **Medium**: 50,000 daily bird limit, 50 premises limit.
- **High**: 100,000 daily bird limit, 100 premises limit.

To clarify, those premises reporting infection would be prioritised above all others for culling, ordered by the date of reporting. For those premises designated for ring culling that were not infected, the order of priority was determined using a distance-based approach, with resources allocated from the outer edge and moving inwards to the centre (an 'outside-to-centre' approach). In other words, following the determination of premises situated within the ring established around a premises reporting infection, distances between all such premises and the infected premises were computed with the premises then culled in descending distance order. Note that all premises in the ring established around the initially reported infected premises had to be treated before moving on to locations that were contained within rings established around the next set of subsequently reported infected premises.

Ring vaccination

For this choice of action, all premises within a specified distance of any premises reporting infection were listed for vaccination. As with ring culling, the ring radii evaluated ranged from 1-10km (in 1km increments). In light of previous research highlighting apparent discrepancies between the vaccine strain and the viruses in circulation in Bangladesh [11] we did not assume perfect vaccine efficacy, but instead set efficacy to 70%. While this is not guaranteed to fully agree with the true efficacy of currently administered vaccines, this considers a general situation where the proposed vaccine possesses a reasonable capability to suppress the circulating strain. We assumed an effectiveness delay of seven days to account for the time required for suitable immune protection to develop after the vaccine was administered (M.G. Osmani and M.A. Kalam, personal communication). With the epidemiological unit of interest being the individual poultry premises, we assumed for successfully vaccinated flocks (i.e. vaccinated premises that did not become infected during the post-vaccination effectiveness delay period) that 30% of the flock remained susceptible to infection (and as a consequence able to transmit infection).

As the vaccination strategies considered here also involved the culling of reported premises, we had to make an assumption regarding how these two aspects should be factored into the resource limits. We were informed that while culling would be carried out by DLS (Department of Livestock Services) staff, vaccines would be administered by the farms themselves in supervision by DLS staff (M.A. Kalam, personal communication). Therefore, we treated these activities as being independent of each other, assigning separate resource limitations to each control action.

The capacity levels that were considered, with culling and vaccination treated independently, were:

- **Low**: 20,000 daily bird limit, 20 premises limit.
- **Medium**: 50,000 daily bird limit, 50 premises limit.
- **High**: 100,000 daily bird limit, 100 premises limit.

There was no limit on the cumulative number of vaccine doses available. An outside-to-centre resource allocation prioritisation approach was used for vaccination, matching the ring culling prioritisation procedure.

Active Surveillance

A total of four active surveillance strategies were compared based on two distinct types of implementation. In model simulations of these initiatives, premises undergoing active surveillance had their notification delay reduced from seven to two days. A two day delay was chosen, and not a larger reduction to a single day or the complete removal of the reporting delay, to align with the shortest delay realistically attainable under ideal conditions. Such a presumption has been made in prior studies [26], and accounts for the fact a flock can be infectious before clinical signs of H5N1 infection are observed, which may not be immediate even when active surveillance procedures are in place [22]. Note that there were no other control actions in place beyond this and the culling of flocks at premises reporting infection (which abided by the previously discussed capacity limitations).

The first two surveillance strategies we consider are reactive in nature. This involved premises within a given distance of premises reporting infection undergoing active surveillance. We imposed a limit on the number of premises that could be treated in this way. Thus, when resource thresholds were exceeded only those premises deemed to be of higher priority underwent active surveillance, with the following two prioritisation strategies studied: (i) 'reactive by distance', with premises ordered by distance to the focal premises, nearest first (i.e. inside-to-out approach); (ii) 'reactive by population', with premises ordered in descending flock size order. For these schemes the ring size for active surveillance was set to be 500m. The three capacity settings used were as follows:

- **Low**: 25 premises per outbreak
- **Medium**: 50 premises per outbreak
- **High**: 100 premises per outbreak

The next two surveillance strategies are proactive approaches, with a specified proportion of premises within the Dhaka division selected by some designated criteria to undergo constant active surveillance. The two criteria evaluated here were: (i) 'proactive by population', ranking all premises in descending flock size order, (ii) 'proactive by premises density', for each premises we computed the total number of other premises within a distance of 500m, with all premises then ranked in descending order. The coverage levels considered were:

- **Low**: 5% coverage
- **Medium**: 10% coverage
- **High**: 25% coverage

Simulation outline

The simulation procedure employed here used the Sellke construction [27]. A desirable characteristic of this framework is that the inherent randomness of an epidemic realisation can be encoded at the beginning of the simulation with a random vector Z of Exp(1) distributed resistances. Once calculated, the resultant epidemic can be constructed from the deterministic solution of the infection process and removal (i.e. culling) times. Therefore, this method provides improved comparisons of interventions, with direct comparison of a collection of control measures achieved by matching values of Z at the epidemic outset.

Choice of control policy based on outbreak origin

For this series of simulations we were interested in elucidating the intensity of control actions necessary to minimise epidemic severity based on the district an outbreak originated in, plus how this differed between the two fitted models with their contrasting premises-to-premises transmission dynamics. To be able to ascertain the true impact of outbreak origin on the epidemic outcomes of interest we assumed premises infection was predominately driven by premises-to-premises transmission, with no infection of premises arising due to external factors. As a consequence, the background spark term ϵ was set to zero in all runs, while in each run an initial cluster of three infected premises was seeded in one of the 18 districts situated within the division (see Fig. 1).

For each culling, vaccination, and active surveillance management action we performed 1,000 simulation runs with the wave 2 fitted transmission model and between 500 to 1,000 simulation runs with the wave 5 fitted transmission model. A consistent set of distinct sampled parameter values (obtained previously via MCMC) and initial seed infection locations were used across these runs to aid intervention comparisons. The particular control objectives of interest here were focused on either reducing the expected length of an outbreak, or minimising the likelihood of an outbreak becoming widespread. To this end, the summary outputs analysed for this scenario were as follows: (i) mean outbreak duration, (ii) probability of an epidemic (where we subjectively define an outbreak as an epidemic if there are infected premises in five or more districts, with the total number of infected premises exceeding 15).

Choice of control policy in presence of external factors

Our second scenario of interest was determining the optimal control strategy when an outbreak is ongoing and infection may arise anywhere within the division, in addition to premises-to-premises transmission dynamics. With regards to this objective these simulations did incorporate the background spark term ϵ, with a single initial infected premises placed anywhere in the division.

We stipulated a simulated outbreak to be complete once a specified number of consecutive infection-free days had occurred. For the wave 2 fitted model, a value of 28 days gave a simulated median epidemic length (using infected premises culling only, with reporting to culling times weighted by the empirical probability mass function) that corresponded well with the data (Fig. 2(a)). On the other hand, a 14 day period with no premises becoming infected was more suitable for the wave 5 fitted model (Fig. 2(b)), with runs using the 28 day infection-free condition giving, in general, longer outbreak periods than the observed data (Fig. 2(c)). As a consequence, the infection-free condition values were set to 28 days and 14 days for runs with the wave 2 and 5 fitted models respectively.

For each poultry-targeted management action we performed 1,000 simulation runs with the wave 2 fitted transmission model and 500 simulation runs with the wave 5 fitted transmission model. To aid intervention comparisons across the runs we again used a consistent set of sampled parameter values and initial seed infection locations. The control objectives of interest in this scenario were again focused on outbreak length and size. In particular, either increasing the chance of an outbreak being short, maximising the likelihood of an outbreak remaining below a specified size, or minimising the number of poultry destroyed as a result of culling. The particular summary statistics that we therefore chose for these control objectives were as follows: (i) outbreak duration t being 90 days or less, (ii) outbreak size I not exceeding 25 infected premises, (iii) mean number of poultry culled.

Results

Choice of control policy based on outbreak origin

Here we consider management of outbreaks whose sole viable route of transmission is premises-to-premises. We establish the severity of control or type of surveillance policy that should be implemented to minimise epidemic duration or probability of a widespread outbreak, dependent upon the district of outbreak origin and capacity constraints.

Culling and vaccination

In the event of outbreaks with wave 2 type transmission dynamics, regardless of the district of introduction, for minimising the epidemic probability we observe the optimal ring cull radius increases under less restrictive capacity constraints (Fig. 3(a)). If capacities are low, then 1km-3km radius ring culling was found to be optimal for most districts (Fig. 3(a), left panel). As capacities increase, we observe a slight increase in the optimum radius, with 8-10km ring culling optimal for outbreaks occurring in some districts (Fig. 3(a), right panel).

A similar effect was observed when considering vaccination as a control strategy (Fig. 3(b)). However, for some districts, in conjunction with low and mid-level vaccination capacities, vaccination was not found to decrease the probability of epidemic take off, with solely culling those premises reporting infection preferred (Fig. 3(b), left and middle panels). In general, optimal vaccination radii for each capacity level were found to be larger than optimal ring culling radii, possibly owing to a delay in onset of immunity. Qualitatively similar outcomes are observed across the tested transmission models and capacity constraints when the objective is to minimise expected outbreak duration (Figs. S2 and S3).

When analysing the impact of control policies to minimise epidemic risk for outbreaks with wave 5 transmission dynamics, we observe a different effect. In this case, optimal ring culling radii were higher than optimal vaccination radii for many districts, even when capacities to implement control were high (Fig. 4). In low capacity circumstances the epidemic source made scant difference to the chosen ring culling size, typically 1km (Fig. 4(a), left panel). This did not hold under a high resource capacity. Outbreaks emerging in central and northern districts typically required upper radius values of 7km or 8km, while the western district of Rajbari (east) required the 10km upper limit of the range of values explored here. In the event of an outbreak beginning in one of the remaining districts only localised ring culling of 1km or 2km was suggested, though we observe a ring cull of some form was always found to be preferred to only culling infected premises (Fig. 4(a), right panel).

On the other hand, regardless of capacity constraints, ring vaccination did not improve on merely culling infected premises for outbreaks beginning in northern and southern districts, while central districts typically only required a coverage radius of 5km or less (Fig. 4(b)).

As a cautionary note, sensitivity analysis of the variations in the control objective metrics against intervention severity (for outbreaks beginning in a given district) revealed these to be small, especially under vaccination measures (Figs. S4 to S7).

Active surveillance

We now investigate the extent to which H5N1 outbreak burden in the Dhaka division of Bangladesh may be reduced through active surveillance. As described above, we consider implementation of both proactive and reactive surveillance strategies. Our model indicates that, regardless of outbreak wave and location of outbreak, proactive surveillance schemes were optimal across all capacity scenarios and objectives being optimised. Additionally, independent of the source district for the outbreak, higher capacity thresholds usually led to greater reductions in outbreak length and size relative to the scenario where no active surveillance scheme was utilised (Fig. 5 and Fig. S8).

For wave 2 transmission dynamics, the ‘proactive by population’ surveillance strategy was found to be optimal for all capacities and districts, with the exception of the district of Narshingdi when the capacity for active surveillance implementation is high. In this instance, if we are interested in minimising outbreak duration, ‘proactive by premises density’ surveillance should be implemented, whilst ‘proactive by population’ surveillance should be used if we wish to minimise the likelihood of an epidemic (Fig. 5(a) and (Fig. 5(b), right panels). Similar outcomes were obtained for outbreaks with wave 5 type transmission dynamics where, irrespective of the district where the outbreak originated, the ‘proactive by population’ strategy was always selected as the optimal action (Fig. S8).

Choice of control policy in presence of external factors

In this section, we consider the impact of control in the Dhaka division in the event of external introductions of disease from the surrounding divisions. In this instance, we determine the control or surveillance policy that should be implemented across all districts in the division that minimises the epidemic duration, outbreak size or the number of poultry culled.

Culling and vaccination

For control objectives targeting outbreak length and magnitude we ascertained that ring culling typically outperformed ring vaccination, with qualitatively similar outcomes acquired for our two distinct transmission models (Figs. 6 and S9). We found that, even when vaccination capacity was high, ring culling resulted in a lower likelihood of long duration outbreaks and fewer premises becoming infected.

For ring culling there was evidence of a performance hierarchy across the three tested capacity constraints Figs. 6(a) and 6(c). For any given ring size a high capacity allowance generally outperformed a medium capacity allowance, which in turn outperformed a low capacity allowance. Further, under high control capacity resource availability each incremental increase in the radius size generally led to modest improvements in the summary output of interest (at least up to the 10km upper limit in place here). In contrast, for low and medium capacity thresholds the optimal radius size varied dependent upon the objective of interest. Such a relationship was less apparent for vaccination. For the epidemic duration control metric in particular, irrespective of the transmission dynamics we identified little variation in this measure between the three capacity constraints across all tested ring sizes and also relative to only culling infected premises Figs. 6(b) and 6(d). Comparable outcomes were found when optimising the epidemic size objective of $I \leq 25$ (Fig. S9).

However, if our objective were to minimise the total number of poultry culled, we found that vaccination was, in all instances, preferred over ring culling (Fig. 7). Incremental increases in vaccination radius size under each set of control capacity conditions were found to cause modest improvements with regards to this objective. Specifically, a 9km or 10km ring was optimal across all capacities and both transmission models. On the other hand, pursuing a ring culling strategy in combination with this control objective results in the best performing action being either no culling beyond infected premises or a ring cull of 1km (Fig. 7). Under wave 2 type transmission dynamics, high capacity ring culling results in the largest number of poultry culled, particularly when implemented at large radii (Fig. 7(a)). For wave 5 transmission dynamics the opposite effect is seen (Fig. 7(c)). The larger expected size of outbreaks in these circumstances means that low capacity ring culling proves insufficient to control the outbreak, resulting in a much larger number of poultry being culled than for higher capacities.

Active surveillance

Investigating the effectiveness of active surveillance against H5N1 HPAI under this transmission setting, a collection of common trends were obtained across the three control objectives (outbreak duration being 90 days or less, outbreak size not exceeding 25 premises, minimising mean number of poultry culled) and two disease transmission models analysed.

Irrespective of the objective being scrutinised, the most effective active surveillance policy was the 'proactive by population' scheme, with this conclusion being consistent under either wave 2 or wave 5 type transmission dynamics (Figs. 8(a) to 8(c)). Additionally, increased availability of resources for control raised the performance of this kind of action. This is typified when examining the outbreak duration objective of $t \leq 90$. Under the wave 2 transmission model this rose from 0.55 (low capacity) to 0.61 (high capacity), whereas with no active surveillance in use the probability was only 0.51. Such effects were even more stark for the wave 5 transmission model, with outbreaks being more likely to spread rapidly and have enhanced longevity under these dynamics. With an initial value of 0.38 when no active surveillance was used, this rose to 0.46 for low capacity levels, reaching 0.58 under high capacity conditions. This represents an approximate 50% improvement over having no control. The remaining control objective measures saw similar improvements as capacity constraints were weakened.

Although the 'proactive by premises density' strategy offers notable improvements under less stringent capacity constraints, it was not as effective as the population-based targeting measure. This is exemplified by the discrepancy between the two typically growing with enlarged capacity thresholds. For example, the difference grew from 0.02 (at low capacity) to 0.04 (at high capacity) for $t \leq 90$ using the wave 2 transmission model, and from 0.07 (at low capacity) to 0.11 (at high capacity) for $I \leq 25$ using the wave 5 transmission model. A further drawback of the 'proactive by premises density' strategy was that under low control capacity levels it struggled to beat either reactive surveillance policy (Fig. 8).

Comparing the two reactive strategies we found their performance differential to be minor. Despite offering marginal benefits over having no active surveillance policy in use, they did not bring about noticeable improvements towards the desired goal under more relaxed capacity constraints (Fig. 8). The observation of 'proactive by population' outperforming 'proactive by premises density', and the two reactive strategies only being a slight improvement compared to having no active surveillance, is also evident when comparing the complete premises outbreak size distributions (Fig. S10). For a full listing of values related to the features raised see Tables S10 to S12.

Discussion

This study explores the predicted impact of a variety of intervention methods, namely culling, vaccination and active surveillance, for mitigating the impact of HPAI H5N1 outbreaks among poultry within the Dhaka division of Bangladesh. Informed via a mathematical and computational approach, it emphasises how knowledge of both disease transmission dynamics and potential resource limitations for implementing an intervention can alter what are deemed the most effective actions for optimising specific H5N1 influenza control objectives. Likewise, we saw differences in policy recommendations when comparing alternative control objectives to one another. This corroborates previous work that showed establishing the objective to be optimised is pivotal in discerning the management action that should be enacted [28], whilst underlining the potential pivotal role mathematical modelling has in providing decision support on such matters.

For circumstances where transmission is exclusively premises-to-premises, we found considerable variation in the preferred control strategy dependent upon the spatial location of the source of the outbreak, the relationship between risk of transmission and between premises distance (examined here by comparing the wave 2 and wave 5 transmission models), and the capacity restrictions that are in place. Although there was a common trend of increasing the suggested radius of an intervention ring zone for less stringent capacity settings, solely culling infected premises was sometimes expected to be the best course of action when both vaccination and ring culling were considered. This is strongly exhibited in the case of reducing the likelihood of a widespread outbreak for an infection with wave 5 type transmission dynamics, with additional ring vaccination deemed ineffective for the majority of district origin locations. In such cases, it may therefore be necessary to consider alternative intervention measures other than vaccination, such as strict movement measures, to further reduce the risk of disease spread. Given insight into the exact outbreak circumstances, this shows the potential benefits of having flexibility to adapt the intervention that is ratified.

Under situations where external factors have a meaningful impact on the transmission dynamics, we found that the preferred intervention strategy was highly dependent upon the objective of the control policy. If we are interested in either minimising outbreak duration or the number of infected premises, ring culling is, in general, preferred to vaccination. This may be a result of the assumptions of a seven day delay from vaccination to immunity and a 70% vaccine efficacy. However, vaccination proves optimal when minimising the number of poultry culled, subject to the previously stated assumptions. Furthermore, We observe effects of capacity becoming apparent for rings of over 4km, as under limited capacity interventions applied beyond this rather local scale do not demonstrate additional increases in effectiveness.

Robustness of these outcomes to alternative vaccine efficacy and effectiveness delay assumptions merits further investigation. Also of interest is that for both models with differing transmission behaviour qualitatively similar conclusions were generally found, possibly due to the fact that although the relative likelihood of premises-to-premises disease transmission (with respect to distance) was well understood, the threat of any premises within the division becoming infected at any time resulted in this factor becoming less influential.

It is vital that the area covered by ring based control methods is selected to only be as large as necessary. If set too small then other premises just outside the intervention zone may become infected, which would have been contained had harsher measures been imposed. However, the use of widespread pre-emptive culling based on defined areas around an outbreak has been shown to be very difficult to implement effectively in developing countries. Enforcing wide area culling can alienate farmers if healthy birds are destroyed, or inadequate compensation is provided or is provided too late. This loss of poultry owner cooperation can be counter-productive, leading to resentment and resistance to further control measures [8].

In terms of active surveillance procedures, a consistent outcome in all settings was the superior performance of proactive schemes, that constantly monitor a predetermined set of premises based on selective criteria, over reactive schemes, which are only enforced once an outbreak has begun. In particular, proactive schemes focused on monitoring the premises with the largest flocks were the most successful, with larger coverage levels strengthening performance outcomes. One caveat of our modelling framework is potential discrepancies between premises in the enforcement of biosecurity protocols have yet to be considered. If premises with larger flocks were to have tighter biosecurity protocols, potentially reducing the notification delay relative to other premises (i.e. below seven days), this may curtail the performance of population based surveillance measures.

Surveillance methodology is a discipline requiring greater attention. With its purpose, in this particular context, being early detection of the introduction and spread of H5N1 HPAI viruses, active surveillance does not have to be restricted to only looking for clinical signs of disease within poultry flocks. It may be used to trace the likely chain of transmission, oversee value chains involving different poultry products to ascertain if there is a particular section of the system where biosecurity is compromised, and monitor trade and marketing links to track the genetic diversity of circulating strains [29, 30]. Such endeavours will in turn contribute towards the standardisation of sampling, testing, and reporting methods, bolstering full-genome sequencing efforts and encouraging sharing of isolates with the scientific community [31].

An alternative focal point for control, not explicitly included here, is trade and live bird markets (LBMs). In the event of disease outbreaks among poultry both farmers and traders face economic losses. In order to reduce such loss they may modify their practices, altering the structure of the trade networks. In turn, these changes may modify the disease transmission dynamics and possibly facilitate additional spread [32].

Equally, the high density and variety of avian hosts in LBMs supports the maintenance, amplification and dissemination of avian influenza viruses, whilst providing frequent opportunities for inter-species transmission events. In a meta-analysis of before-after studies, to assess the impact of LBM interventions on circulation of avian influenza viruses in LBMs and transmission potential to humans, Offeddu et al. [33] determined that periodic rest days, overnight depopulation and sale bans of certain bird species significantly reduced the circulation of avian influenza viruses in LBMs. Furthermore, prolonged LBM closure reduced bird-to-human transmission risk. Developing a theoretical model with trade and LBMs included would allow us to validate these findings.

The analysis presented here did not consider the role of domestic ducks, due to the low quantity of poultry premises within the Dhaka division recorded as having ducks present. Nonetheless, at a national level domestic ducks are part of an intricate animal production and movement system, which may contribute to avian influenza persistence [34]. Ducks raised in free-range duck farms in wetland areas have considerable contact with wild migratory birds in production sites, and then with other poultry animals in LBMs. Furthermore, influenza viruses of the H5 subtype typically persist in ducks with very mild or no clinical signs [35–39], affecting epidemic duration and spread. Thus, if applying this work to other regions of Bangladesh, or scaling it up to encompass the entire country, domestic ducks warrant inclusion within the model framework.

This initial analysis can be extended naturally in a number of additional ways to those already mentioned. While we considered conventional control strategies used to combat avian influenza outbreaks among poultry, namely culling, vaccination and active surveillance, one could compare these traditional schemes with innovative direct interruption strategies that modify the poultry production system [40]. An example would be intermittent government purchase plans, so that farms can be poultry-free for a short time and undergo disinfection. Another is to model restrictions on species composition. This aims to synchronise all flocks on a premises to the same birth-to-market schedule, allowing for disinfection of the premises between flocks. A separate direction for further study is to understand whether the intensification of farming systems, which can alter the demography and spatial configuration of flocks, requires the severity of previously established control protocols to be amended to prevent a small-scale outbreak developing into a widespread epidemic. Such an analysis may be realised by modifying the current model framework to classify premises based on flock size and whether they utilise intensive and extensive methods, with distinct epidemiological parameters for each group.

The extent to which other premises prioritisation schemes for administering the intervention of interest influences the results also warrants further examination. For the culling and vaccination controls deliberated here we assumed premises were prioritised by distance, from the outer edge of the designated ring control size inwards. Alternative prioritisation strategies that may be considered, subject to availability of the necessary data, include ordering by flock size (in either ascending or descending order), by between-premises flock movement intensity or prioritising by value chain networks. In the case of active surveillance, rather than a fixed, pre-determined policy, extra flexibility can be included by allowing for differing pre- and post-outbreak strategies. Ultimately, public-health decision making generally necessitates the real-time synthesis and evaluation of incoming data. Optimal decision making for management of epidemiological systems is often hampered by considerable uncertainty, with epidemic management practices generally not incorporating real-time information into ongoing decision making in any formal, objective way. An adaptive management approach could be implemented to account for the value of resolving uncertainty via real-time evaluation of alternative models [28, 41].

To conclude, through the use of mathematical modelling and simulation, the results of this paper illustrate some general principles of how disease control strategies of H5N1 in the Dhaka division of Bangladesh should be prioritised and implemented when having to account for resource availability. We highlight how targeting of interventions varies if it is believed transmission is predominately premises-to-premises, versus the scenario where importations and other external factors are included. Most importantly, based on this consideration, targeted active surveillance can significantly reduce the scale of an epidemic as long as the appropriate choice between reactive and proactive strategies is made. They also indicate that reactive culling and vaccination control policies should pay close attention to this factor to ensure intervention targeting is optimised. Consequently, we advocate that much more attention is directed at identifying ways in which control efforts can be targeted for maximum effect.

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Data availability

Data are available from FAO Regional Office for Asia and the Pacific who may be contacted at FAO-RAP@fao.org.

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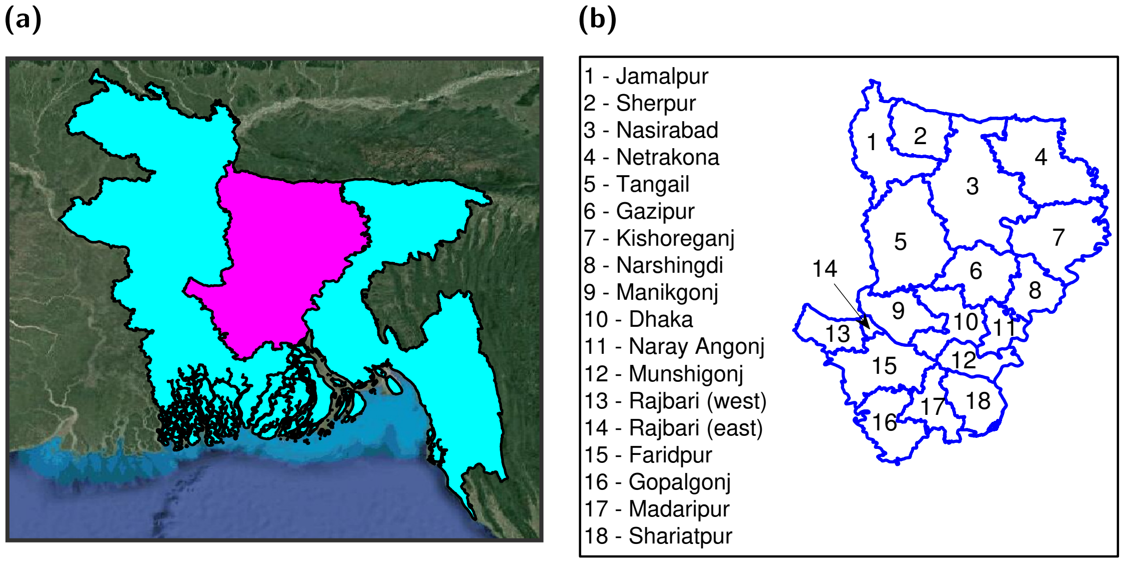

Fig. 1: Dhaka administration region locator maps. **(a)** Locator map depicting the location of Dhaka division, shaded in magenta, within Bangladesh, shaded in cyan. **(b)** Locator map naming each district that is contained within the Dhaka division.

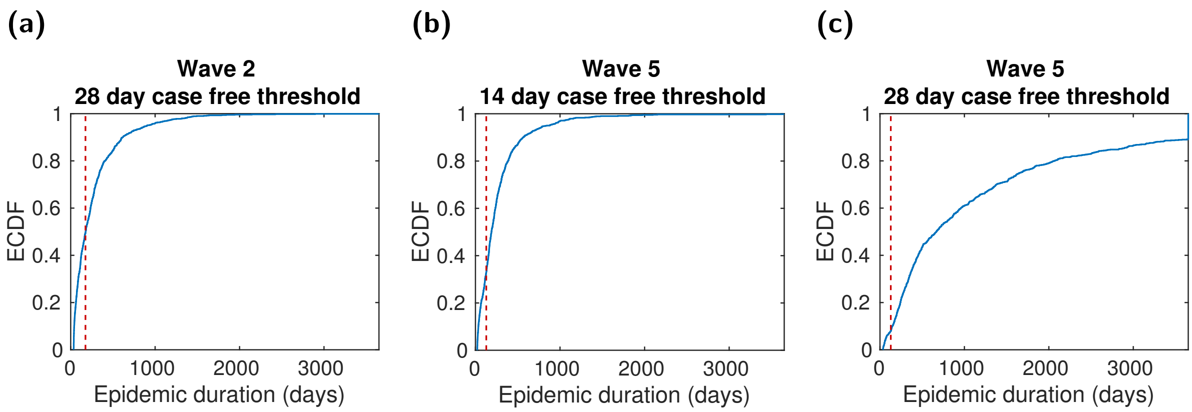

Fig. 2: ECDF for epidemic duration from simulations of the specified transmission model, with the given number of consecutive infection-free days required for an outbreak to be deemed as completed. All simulations used infected premises culling only (no additional controls were in place), with reporting to culling times weighted by the empirical probability mass function. The following ECDFs were constructed using 1,000 simulated realisations: **(a)** Wave 2, 28 day threshold value; **(b)** wave 5, 14 day threshold value; **(c)** wave 5, 28 day threshold value. The threshold values for number of infection-free days signifying the end of an outbreak were subsequently set to 28 days and 14 days for runs with the wave 2 and 5 fitted models respectively.

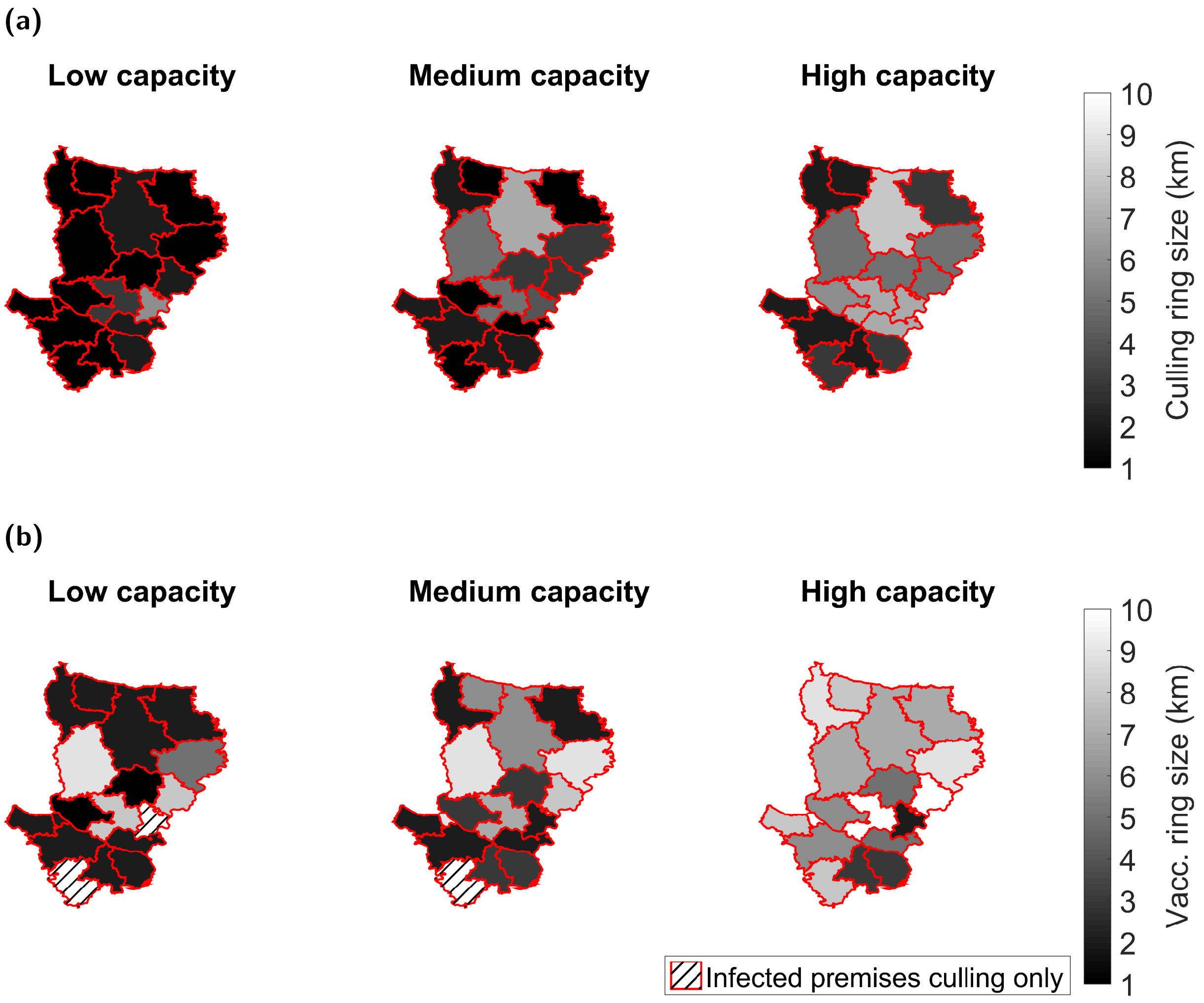

Fig. 3: Maps displaying the ring range that optimises minimising epidemic probability with respect to district of outbreak origin and control capacity level, under wave 2 type transmission dynamics. For each combination of control capacity level, district of outbreak origin and control type 1,000 simulation runs were performed. Hatching of a district indicates the preferred strategy was culling infected premises only, while solid shading corresponds to the ring size determined as the optimal severity of response against outbreaks that originally emerged in that district. Lighter shading corresponds to a larger ring culling region. Types of control tested were **(a)** ring culling, and **(b)** ring vaccination. For full results see Table S2.

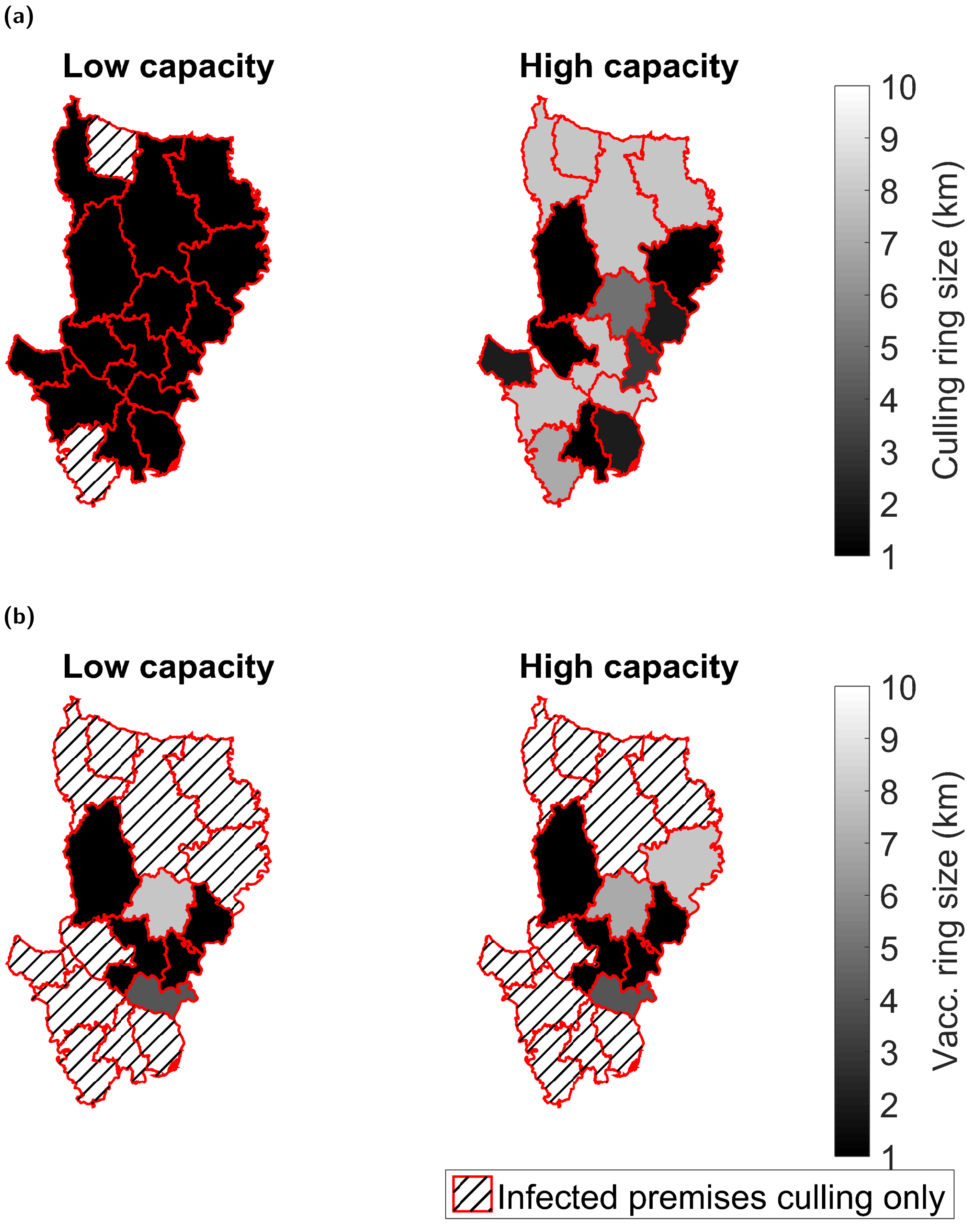

Fig. 4: Maps displaying the ring range that optimises minimising epidemic probability with respect to district of outbreak origin and control capacity level, under wave 5 type transmission dynamics. For each combination of intervention method and district of outbreak origin 1,000 simulation runs were performed. Hatching of a district indicates the preferred strategy was culling infected premises only, while solid shading corresponds to the ring size determined as the optimal response against outbreaks that originally emerged in that district. Lighter shading corresponds to a larger intervention region. Types of control tested were **(a)** ring culling, and **(b)** ring vaccination. For full results see Table S4.

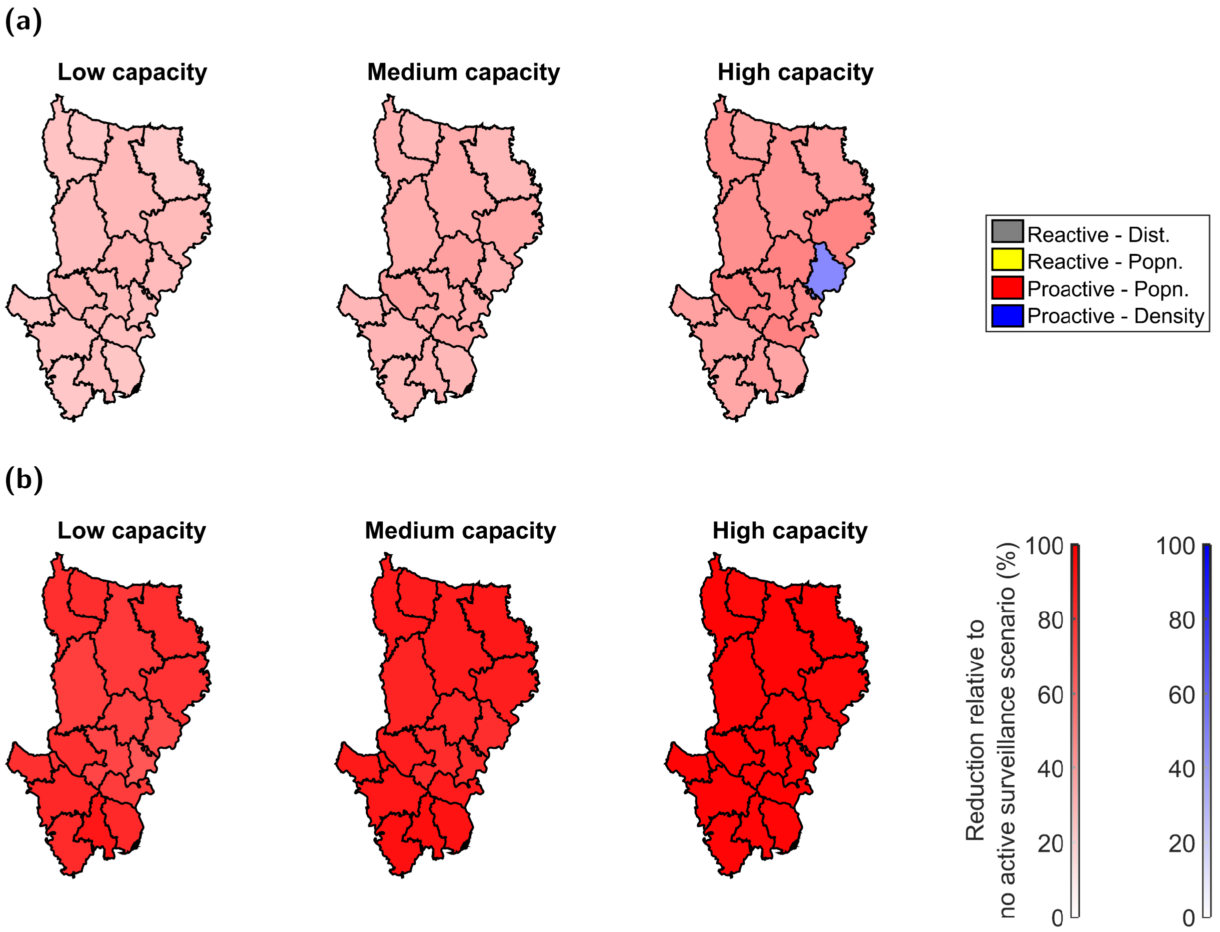

Fig. 5: Maps displaying the preferred active surveillance strategy to optimise control objectives with respect to district of outbreak origin and capacity setting, for outbreaks with wave 2 type transmission dynamics. For each combination of active surveillance method and district of outbreak origin 1,000 simulation runs were performed. District colour corresponds to the active surveillance strategy determined to be optimal for countering outbreaks originating from that district (grey - 'reactive by distance', yellow - 'reactive by population', red - 'proactive by population', blue - 'proactive by premises density'). Transparency coincides with the reduction in the objective metric relative to the scenario where no active surveillance was utilised, with completely transparent corresponding to a 0% reduction (no improvement) and completely opaque corresponding to a 100% reduction. **(a)** Minimising average outbreak duration control objective - 'proactive by population' scheme was generally preferred, although we found discrepancies in the best scheme dependent upon the control capacity setting. **(b)** Minimising the probability of an epidemic control objective - 'proactive by population' scheme was found to be preferred in all cases when optimising for this aim. For full results see Tables S6 and S7.

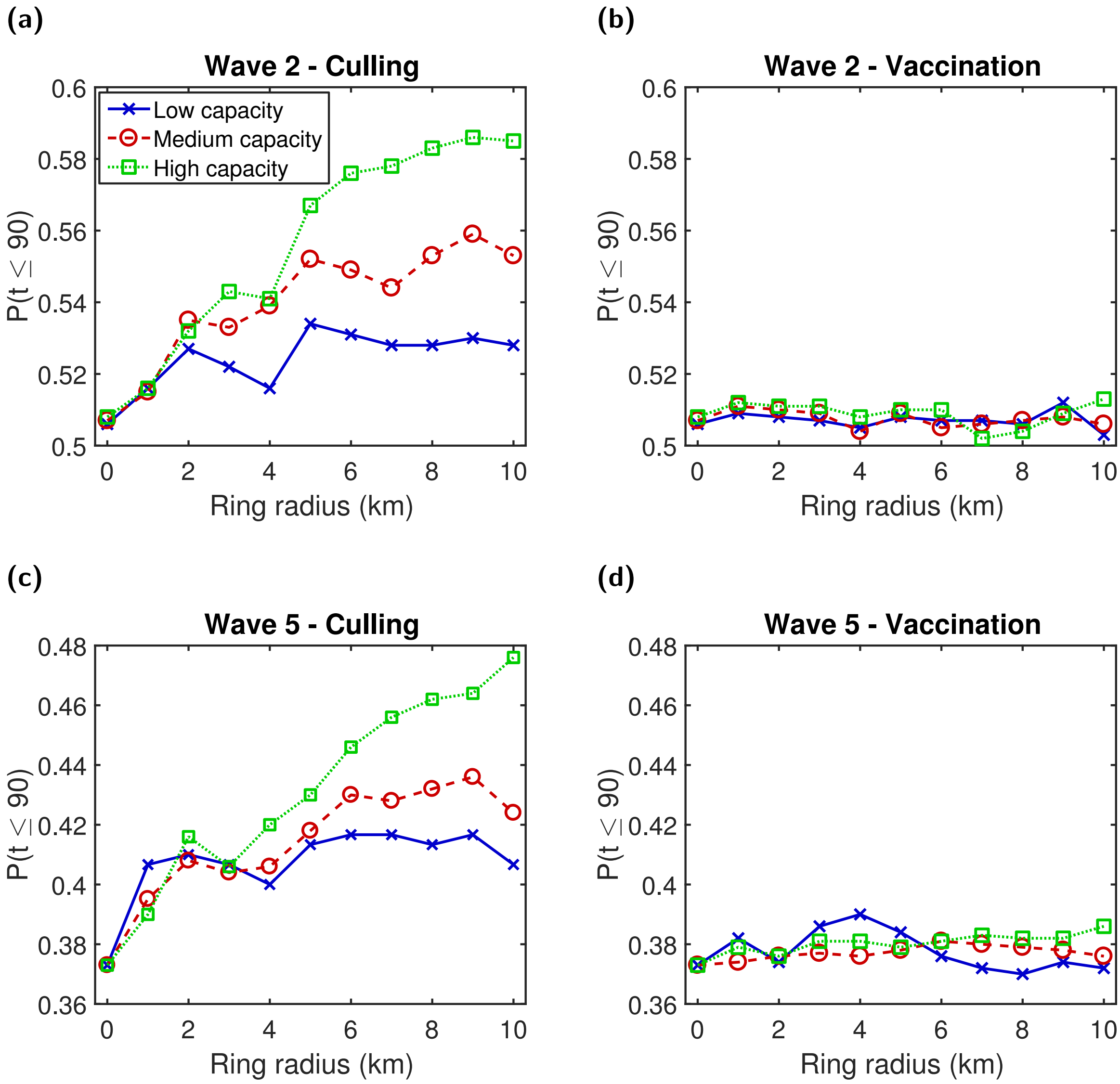

Fig. 6: Predicted probability of outbreak duration (t) being 90 days or less for different ring culling and vaccination radii. For each transmission model and control method combination, the three capacity settings of interest, low (solid blue line, crosses), medium (dashed red line, circles), and high (dotted green line, squares) displayed disparate behaviour. **(a)** Wave 2 - culling; **(b)** wave 2 - vaccination; **(c)** wave 5 - culling; **(d)** wave 5 - vaccination. Results are averaged over 1,000 simulations and 500 simulations for wave 2 and wave 5 type transmission dynamics respectively.

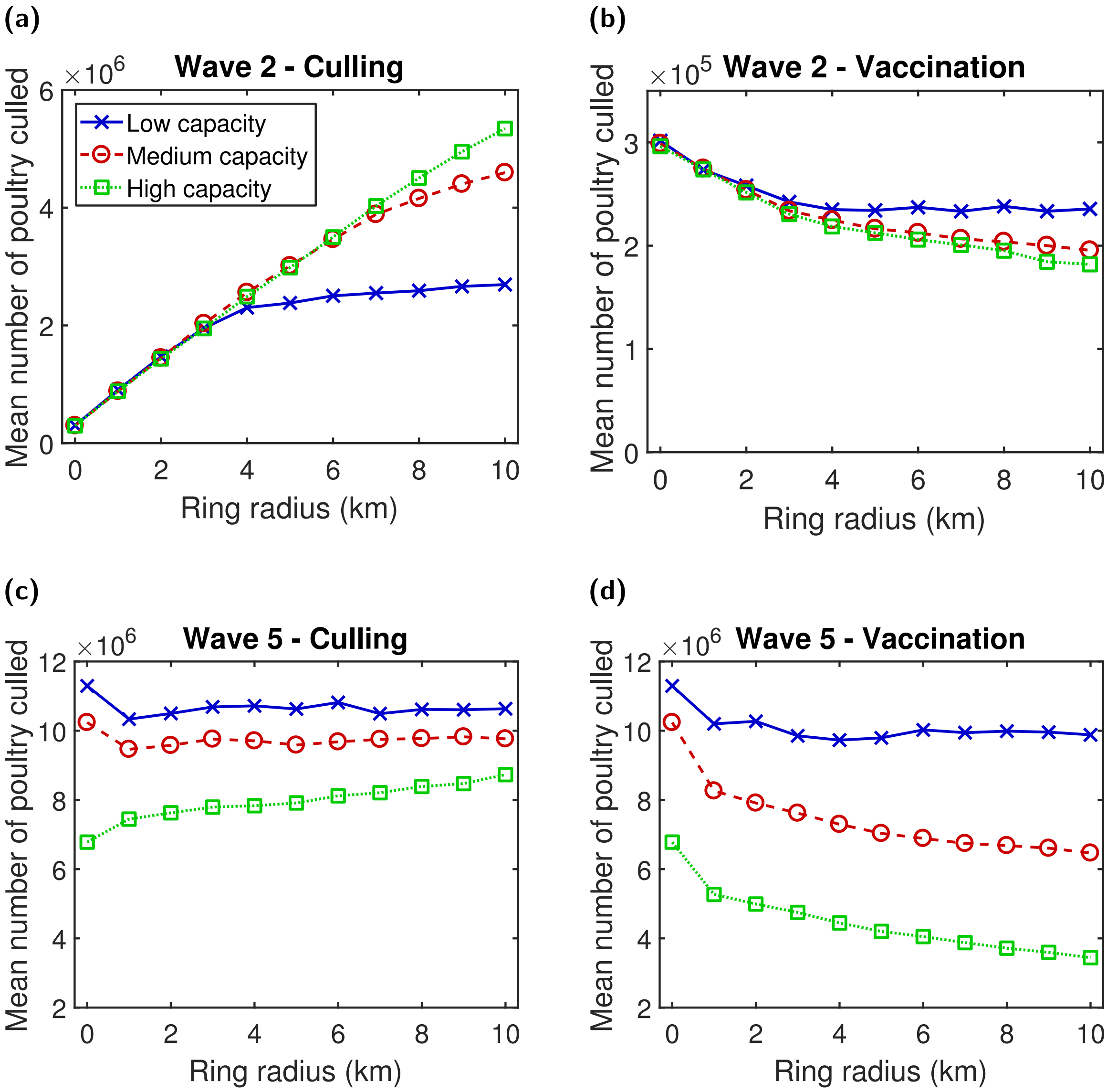

Fig. 7: Mean number of poultry culled for different ring culling and vaccination radii. The three capacity settings of interest were low (solid blue line, crosses), medium (dashed red line, circles), and high (dotted green line, squares). If pursuing a ring culling strategy, either no culling beyond infected premises or a ring cull of 1km were deemed optimal. For a ring vaccination strategy, a 9km or 10km ring was selected across all capacities. **(a)** Wave 2 - culling; **(b)** wave 2 - vaccination; **(c)** wave 5 - culling; **(d)** wave 5 - vaccination. Results are averaged over 1,000 simulations and 500 simulations for wave 2 and wave 5 type transmission dynamics respectively.

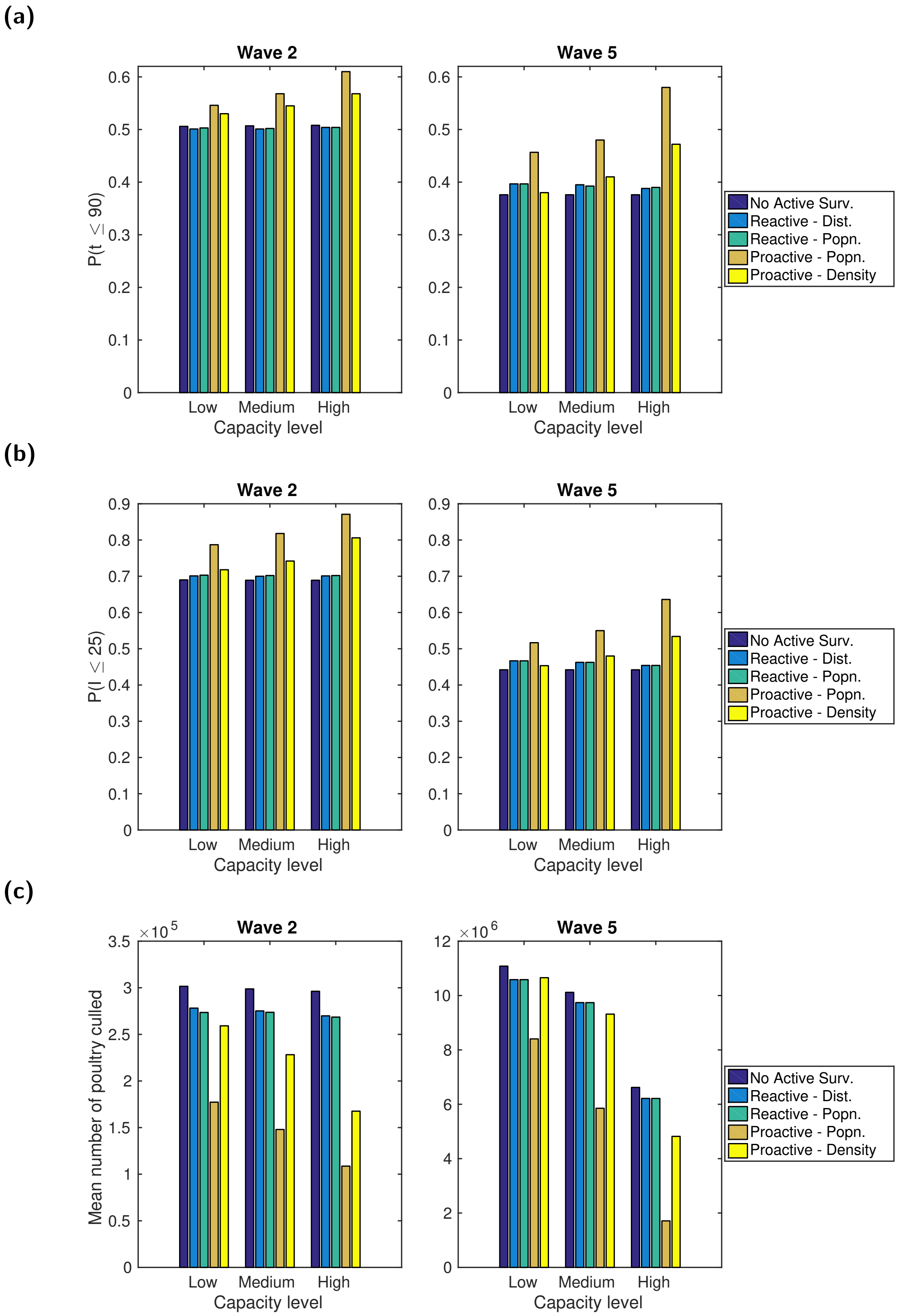

Fig. 8: Bar plots comparing the impact of different active surveillance strategies on specific control objectives. For each combination of transmission model, resource restrictions and active surveillance strategy we performed between 500 and 1,000 simulation runs. The control objectives were: **(a)** predicted probability for outbreak duration t being 90 days or less; **(b)** predicted probability for outbreak size I not exceeding 25 premises; **(c)** mean number of poultry culled. For both wave 2 and wave 5 transmission dynamics the 'proactive by population' surveillance strategy was found to be optimal for all control objectives considered, irrespective of the capacity limitations. Full values are given in Tables S10 to S12.