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Highlights

- We characterised the four past influenza pandemics by their transmissibility and infection-severity
- We projected the benefits of different preparedness policy against the four historic influenza pandemics
- Immunisation against pandemic influenza, in presence of effective antiviral drugs, does not have positive net-present value across all pandemic scenarios considered
- In absence of effective antiviral drugs, vaccination was most beneficial if started sufficiently early and covered sufficiently large number of people
- Comparing the two vaccine programmes, the responsive-purchase immunisation policy allowed a longer timeframe and lower coverage to attain the same benefit as the pre-purchase immunisation policy

Are we prepared for the next influenza pandemic? Lessons from modelling different preparedness policies against four pandemic scenarios

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Abstract

In the event of a novel influenza strain that is markedly different to the current strains circulating in humans, the population have little/no immunity and infection spreads quickly causing a global pandemic. Over the past century, there have been four major influenza pandemics: the 1918 pandemic ("Spanish Flu"), the 1957-58 pandemic (the "Asian Flu"), the 1967-68 pandemic (the "Hong Kong Flu") and the 2009 pandemic (the "Swine flu"). To inform planning against future pandemics, this paper investigates how different is the net-present value of employing pre-purchase and responsive- purchased vaccine programmes in presence and absence of anti-viral drugs to scenarios that resemble these historic influenza pandemics. Using the existing literature and in discussions with policy decision makers in the UK, we first characterised the four past influenza pandemics by their transmissibility and infection-severity. For these combinations of parameters, we then projected the net-present value of employing pre-purchase vaccine (PPV) and responsive-purchase vaccine (RPV) programmes in presence and absence of anti-viral drugs. To differentiate between PPV and RPV policies, we changed the vaccine effectiveness value and the time to when the vaccine is first available. Our results are "heat-map" graphs displaying the benefits of different strategies in pandemic scenarios that resemble historic influenza pandemics.

Our results suggest that immunisation with either PPV or RPV in presence of a stockpile of effective antiviral drugs, does not have positive net-present value for all of the pandemic scenarios considered. In contrast, in the absence of effective antivirals, both PPV and RPV policies have positive net-present value across all the pandemic scenarios. Moreover, in all considered circumstances, vaccination was most beneficial if started sufficiently early and covered sufficiently large number of people. When comparing the two vaccine programmes, the RPV policy allowed a longer timeframe and lower coverage to attain the same benefit as the PPV policy.

Our findings suggest that responsive-purchase vaccination policy has a bigger window of positive net-present value when employed against each of the historic influenza pandemic strains but needs to be rapidly available to maximise benefit. This is important for future planning as it suggests that future preparedness policies may wish to consider utilising timely (i.e. responsive-purchased) vaccines against emerging influenza pandemics.

Introduction

Influenza is a disease of the upper respiratory tract and the large airways [1] and yearly, approximately one billion people get infected and 290,000 to 650,000 respiratory deaths each year [2]. Influenza types A and B circulate and cause seasonal epidemics of the diseases [2,3]. Influenza A viruses are classified according to the combinations of proteins on the surface of the virus (the hemagglutinin (HA) and the neuraminidase (NA)) and currently circulating type A viruses among humans are A(H1N1)pdm09 and A(H3N2) [2]. Influenza B viruses are broken down into two lineages instead of subtypes with currently circulating strains belonging to either B/Yamagata or B/Victoria lineage [3]. These usually cause a milder influenza infection and are not hosted in animals [4].

Influenza epidemics and pandemics occur as a result of changes in the HA/NA proteins within the structure of the type A virus [5,6]. Changes that can occur between influenza seasons (known as antigenic drift) result in annual epidemics of seasonal influenza, with winter peaks in temperate regions (Fig 2 of [4]). In contrast, when a new influenza A subtype emerges abruptly because of a major shift in the proteins on the virus surface (antigenic shift), pandemics or severe global epidemics of influenza occur [4]. Pandemic influenza is defined as an epidemic of influenza "that occurs worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people". Pandemics often emerge as a consequence of a type A virus circulating in animals, but which represents an influenza strain that is markedly different to circulating strains in humans [2,4,7]. In an environment where most people have no immunity to this new virus subtype, infection can spread quickly and cause serious disease [5].

Over the past century there have been four major influenza pandemics: the 1918 pandemic caused by type A H1N1 virus ("Spanish Flu"), the 1957-58 pandemic caused by the type A H2N2 virus (the "Asian Flu"), the 1967-68 pandemic caused by the type A H3N2 virus (the "Hong Kong flu") and the 2009 pandemic caused by a type A H1N1pdm09 virus that was different to circulating type A H1N1 strains at the time (the "Swine flu") [5]. The occurrence of these pandemics illustrates the continuous threat from pandemic influenza and highlights the importance to make thorough preparedness plans for a future pandemic.

Currently existing preparedness measures against pandemic influenza include plans for mass immunisation of the population and for administering antiviral drugs to cases that can reduce the duration and severity of infection [8]. There are two possible mass immunisation strategies against emerging pandemic influenza: pre-purchase (also known as pre-pandemic) vaccine (PPV) strategy or responsive-purchase (also known as pandemic-specific) (RPV) vaccine strategy. The former strategy consists of stockpiling a pandemic vaccine based on a likely pandemic virus that has been identified. PPV can be deployed early in the pandemic but as it is not tailored to the actual circulating pandemic strain, it is expected to be less effective. The second option involves purchasing a vaccine that will be tailored to the actual circulating pandemic strain, and is thus expected to be more effective, but due to manufacturing time will be available sometime after the onset of the pandemic. Using traditional vaccine technology this is anticipated to be 6 months once the pandemic virus is identified. In this paper, in line with our previous work [11], we will refer to these two pandemic preparedness options as pre-purchase vaccine (PPV) and responsive-purchase vaccine (RPV). The interplay between having a quick-and-less effective vaccine (with PPV strategy) or slower-and-more-effective vaccine (with RPV strategy) is the decision that policy

makers are faced with when deciding the best preparedness measure against emerging influenza pandemic. Newer vaccine technology is blurring these lines, with future pandemic specific vaccines potentially available in weeks, rather than months.

Different influenza strains are often characterised by their transmissibility and infection-severity of the infection. Transmissibility can be characterised by the reproduction number (R), defined as the average number of secondary cases generated per typical infectious case. In essence, R describes on average how many persons a case will infect, and a value of R greater than 1 indicates that the infection may grow and persist in the population while a value of R less than 1 indicates that the infection will decline in the population and eventually be eradicated. If R is calculated in a population entirely susceptible to infection (or where an assumption about population susceptibility to infection is made), then R is known as the basic reproduction number (R0). A measure for infection severity or fatality from infection is the case fatality rate or ratio (CFR) that describes the proportion of people who die from the infection among all individuals diagnosed. For the purpose of this work we will use R0 as the measure for influenza transmissibility and CFR to characterise influenza severity or fatality.

In the literature there is a large portfolio of mathematical modelling work that has historically been used to evaluate the impact and cost-effectiveness of different intervention strategies against influenza (e.g. [12-19]). This existing modelling work has largely been focused on evaluating specific pre-purchase immunisation strategies, sometimes with other countermeasures such as antivirals [19] or social distancing [15], against a specific influenza strain. Only one recent study [20] specifically investigated the cost-effectiveness of responsive purchase vaccination by taking into account a 6-month delay in vaccine availability. Recently, a unifying approach that considered different countermeasures against different influenza strains was developed [11]. This work involved extending an existing mathematical model [13], parametrising it for the UK context and combining it with a UK specific economic model. Details of the mathematical model adaptations can be found in the Appendix B of [11] whereas the details of the economic model can be found in Appendix C of [11]. For different combinations of the model parameters that characterised either the features of the influenza strain or the immunisation strategy in presence or absence of antivirals, in [11] a large number of scenarios were explored across different pandemic strains and different preparedness options. This library of results includes most of the scenarios explored in existing modelling studies [12]-[20].

The paper describing that work [11], details the methodology developed and gives an overview of circumstances under which preparedness plans involving different immunisation strategies would be considered good policy options.

In this paper we focus our attention on the scenarios simulated in [11] that are relevant to the past four influenza pandemics. We specifically aim to investigate how different the net-present value is for different preparedness policies in the context of four different strains that best resemble the past four influenza pandemics. To achieve this aim: (a) we used the existing literature to characterise the four existing pandemics by their transmissibility and infection-severity and (b) for each of the four pandemics, we projected the net-present value of PPV and RPV policies in presence and absence of anti-viral drugs for employing in case of such virus strains pandemics.

Methods

We searched the existing literature, and also took advice from policy decision makers at Public Health England, to determine values of R0 and CFR that can characterise respectively the transmissibility and infection-severity of the past influenza pandemics. These are listed in Table 1. For the different combinations of R0 and CFR from Table 1, we used methods described in [11] to explore the net-present value of employing different influenza preparedness policies. The methodology, in [11] and here, included adapting an existing epidemiological model for seasonal influenza transmission and vaccination [12] that was recently made publicly available [21] in the open source programming language R (https://www.r-project.org). Details of the adaptation and model specifics are contained in Appendix B of [11]. The adapted epidemiological model projected the number of susceptible, exposed, infected and recovered individuals. We used UK demography data and published reports of influenza deaths and hospitalisation to transfer from influenza cases to influenza deaths and hospitalisations. These influenza burden outputs were combined with an economic model to project the net-present value (NPV) or net benefit of two different immunisation strategies against pandemic influenza: pre-purchase vaccine (PPV) and responsive-purchase vaccine (RPV) in absence and presence of antiviral drugs. We note that both in [11] and here we calculated the NPV by subtracting the total costs (from the economic model) from the total benefit (from the epidemiological model) for the scenarios considered.

Unlike the work in [11] where a large number of parameters were changed to reflect different influenza strains and vaccination strategies, here we imposed fixed values for many parameters as per Table 2. Specifically, we only changed R0 and CFR values to reflect the characteristics of the influenza pandemics of the twentieth century and we changed the model parameters to account for the two different immunisation policies.

To differentiate between pre-purchase and responsive-purchase vaccine policies, on advice from policy decision makers, we changed the vaccine effectiveness value and the time to when the vaccine is first available (referred to as the time to first vaccination). PPV is stockpiled and therefore available before pandemic emerges, whereas RPV is tailor made to an emerging pandemic and is expected to be available later in the pandemic. Thus we assumed that PPV will be available sooner than RPV whereas RPV is expected to be more effective than PPV; and when considering PPV policy, we set the vaccine effectiveness to be 20% and the time to first vaccination to about 8 weeks, whereas when considering an RPV policy we set vaccine effectiveness to be 60% and the time to first vaccination to 16 weeks. These values were derived in discussion with collaborators within Public Health England and the Department of Health and Social Care as part of our study in [11]. Our results include output "heat-map" graphs displaying the net present value (NPV) of different strategies against five Pandemic Scenarios 1-5 listed in Table 1.

Results

Using existing and established literature, we could stratify the past four influenza pandemics by their rate of transmissibility (R0) and infection-severity (CFR). In the case of the AH1N1 2009 Swine flu pandemic, there are two different CFR values reported in the literature (0.04% and 0.2%) so we considered both of these as separate scenarios. The combinations of R0 and CFR for each of the five Pandemic Scenarios 1-5 are listed in Table 1.

Using an adaptation of the existing epidemiological model [12,21] within the methodology developed in [11] we were able to project the net-present value (NPV) of either PPV or RPV strategies in presence and absence of antiviral drugs if employed across the five Pandemic Scenarios 1-5.

In the presence of effective antivirals, our results suggest that there was no positive NPV in the majority of the scenarios examined, with the exception of scenario 5 and a small window in scenario 4. Specifically, in presence of effective antivirals, both PPV and RPV immunisation strategy have positive NPV if the next pandemic resembles Pandemic Scenario 5 i.e. against an influenza pandemic of the style of the 1918 pandemic that is highly transmissible and with high infection-severity as per Figures 1-5 (c)-(d)). There is also a small window of positive NPV of vaccinating with responsive-purchase vaccine strategy benefit when employed in Pandemic Scenario 4 i.e. against a fast-spreading but not highly fatal influenza pandemic (i.e. of the style of 1967-68 "Hong-Kong" influenza pandemic). This window of positive NPV is present only if the vaccination is started sufficiently quickly and within 28 days of first infection (Figure 4(d)). In Pandemic Scenarios 1-3, which are either not highly transmissible and/or with low infection-severity, in presence of effective antiviral drugs, our results suggest that there is no positive NPV of additional PPV or RPV strategy.

In absence of effective antiviral drugs, there is a window of positive NPV of both PPV and RPV immunisation programme across all five pandemic scenarios we considered. Our simulations suggest that the lowest maximum achievable benefit is from pre-purchase immunisation programme against an influenza that has slow-transmissibility and low infection-severity influenza of the type of the 2009 Swine flu with CFR=0.04% (Pandemic Scenario 1 in Table 1 with results contained in Figure 1(a)). In the case of the other scenarios, where transmissibility and/or infection-severity are higher i.e. Pandemic Scenarios 2-5, the level of positive NPV (i.e. the deep green surface area in the tiles in Figures 1-5(a)-(b)) is dependent on the start of the vaccination and how many people are effectively covered with the immunisation programme. Next, we present the results for each of the Pandemic Scenarios 1-5 in the absence of AV drugs.

Pandemic Scenarios 1 and 2 (2009 "Swine flu" with different infection-severity)

For the Pandemic Scenarios 1 and 2, we are simulating an influenza strain akin to the 2009 Swine Flu with low-transmissibility and either low infection-severity Flu (Pandemic Scenario 1) or high infection-severity (Pandemic Scenario 2). Results are presented respectively in Figure 1(a)-(b) and Figure 2(a)-(b) for the two Pandemic Scenarios. Our results suggest that the strength of the NPV depends on how early is vaccination started and the vaccine coverage level required. Employing RPV policy is less sensitive on this days-to-first-vaccination and coverage level relationship across the range of values we tested. As a consequence, employing an RPV strategy in this scenario has greater NPV compared to an PPV programme (evident from larger area of deep green in Figures 1(b) and 2(b) compared to respective Figures 1(a) and 2(a)).

For example, in Figure 1(b) if RPV strategy is started within 56 days of the pandemic onset, at 30% vaccine coverage level, the NPV is positive and large. For the same combination of days-to-vaccination and coverage level, a PPV strategy will have notably smaller, albeit positive, NPV.

Pandemic Scenario 3 (1957-58 "Asian flu") and Pandemic Scenario 4(1967-68 "Hong-Kong flu")

When simulating the Pandemic Scenario 3 (i.e. with characteristics of the Asian influenza of 1957-58) or Pandemic Scenario 4 (i.e. with characteristics of the 1967-68 Hong-Kong influenza), our results suggest there is a positive NPV of both PPV and RPV strategies in absence of effective antiviral drugs (Figures 3(a)-(b) and Figures 4(a)-(b)). The actual benefit is dependent on how quickly and how effective is the immunisation programme, with either immunisation strategies having a larger positive NPV if vaccination starts sufficiently early and has a sufficient coverage. The exact intrinsic relationship between these depends on the pandemic scenario considered.

For example, when considering PPV strategy employed in Pandemic Scenario 3, for highest positive NPV immunisation needs to start within 70 days at 48% coverage or start within 98 days at 90% coverage for PPV (Figure 3(a))). The required coverage level is lower with an RPV strategy: if immunisation starts within 70 days it requires at least 20% coverage but commencing vaccination at 98 days requires higher coverage level (25%) (Figure 3(b)).

Analogously, preparedness plans to immunise with either PPV or RPV if the next pandemic resembles Pandemic Scenario 4 has positive NPV only if vaccination could start sufficiently early and cover enough people. For example, if PPV commences within 56 days it requires 55% coverage to be beneficial, whereas if it starts at 70 days it requires 60% coverage (Figure 4(a)). The required coverage levels are lower when employing an RPV strategy: if immunisation starts within 56 days it requires 15% coverage, whereas starting at 70 days requires higher (25%) coverage (Figure 4(b)).

Pandemic Scenario 5 (1918 "Spanish Flu")

In Pandemic Scenario 5, when simulating an influenza strain that is highly-transmissible and with high infection-severity, akin to the 1918 Spanish flu, our results suggest that vaccination with either PPV or RPV is beneficial as long as it is started sufficiently early (Figure 5(a)-(b)). RPV strategy has larger range of combinations of coverage/days-to-first-vaccination where NPV is positive than a PPV strategy. Hence, immunisation with RPV can be started later than when employing a PPV policy at the same coverage level: RPV started at 126 days at 30% coverage is beneficial, whereas PPV strategy started at the same time and same coverage level is not (as per Figure 5(a)-(b)).

Discussion

In this paper we utilised previously established mathematical and economic models, to explore when different immunisation policies in presence and absence of antiviral drugs have positive NPV if the next pandemic resembles one of five Pandemic Scenarios that reflect the past four influenza pandemics.

Our results suggest that in presence of a stockpile of effective antiviral drugs, a strategy of mass immunisation with either pre-purchase or responsive-purchase vaccine (PPV or RPV) does not have positive net-present value for all five of the Pandemic Scenarios considered. In contrast, in the absence of effective antivirals, a strategy of mass immunisation with either PPV or RPV has positive net benefit in most of the considered circumstances. In each of the Pandemic Scenarios 1-5, vaccination was most beneficial if started within a certain time

frame and the programme effectively covered sufficient number of people, with RPV policies allowing a longer timeframe and lower coverage to attain the same benefit in comparison to the analogous PPV policy (comparing deep green surface in Figures 1-5(a) with those in corresponding Figures 1-5(b)).

The work presented here is a specific extension of the work in [11]. While in [11] we considered vast combinations of influenza strain characteristics, in that work we did not engage with what influenza strain combinations are plausible in pandemics. In this paper, instead we designed our study around a small number of scenarios that are intrinsically plausible as they resemble historic influenza pandemics. We recognise that the characteristics of future pandemics are difficult to predict given the mutability of the influenza virus and the range of morbidity and mortality experienced in previous pandemics. Although different influenza strains have in previous research been characterised by measures for their transmissibility or infection-severity (e.g. [13,15,16]), using both dimensions to stratify all four previous pandemics and contrast the different preparedness policies against them is, to our knowledge, novel. Finally, there is also novelty in assessing a number of scenarios rooted in historic examples but within the same analytical framework, hence allowing direct comparison between the scenarios. In existing modelling literature, although the same structure of the theoretical framework (i.e. a system of ordinary differential equations parametrised to either fixed or distribution-driven parameters) may have been used, the characteristics of the influenza are crucial in the model calibration, and hence calibrated models are different. Instead, our approach uses the same (calibrated) model and hence makes comparison between scenarios more plausible.

Our findings suggest that responsive-purchase vaccination policy has a bigger window of positive net-present value when employed against each of the historic influenza pandemic strains. This thinking is in line with extensive efforts that are under way to develop more rapidly available effective pandemic specific vaccines rapidly [30-32]. While conventional egg-derived vaccines can suffer from a variety of manufacturing problems, including microbial contamination and poor growth of some human influenza viruses in eggs, leading to potential delays in vaccine supply, cell culture–derived vaccines manufactured from a seed virus however, could be produced rapidly and allow swift responses to an emerging pandemic [32,33]. In addition, because fully cell culture–derived influenza vaccines are more likely to preserve the antigenic structure of the hemagglutinin (HA) antigens, they may even be superior to egg-based vaccines [33]. To date, a Madin-Darby canine kidney (MDCK) cell culture technology has already been licensed for the manufacture of seasonal influenza vaccines in the United States (Flucelvax, Novartis Vaccines), as well as for both seasonal (Optaflu, Novartis Vaccines) and pandemic vaccines (Celtura, Novartis Vaccines) in Europe. Moreover, in a recent simulated (timed) response to a potential influenza pandemic, the use of a synthetic seed virus, containing the HA and neuraminidase (NA) genes from a supplied A/H7N9 virus sequence, was investigated in conjunction with the MDCK cell culture technology. Together, these approaches resulted in impressively rapid vaccine production rates, much faster than currently possible with standard methods [30]. Such vaccine has similarities to the responsive purchase vaccine we are discussing here. Therefore, out analysis sits alongside studies such as [30-33] suggesting that future preparedness policies may wish to consider utilising timely (or responsive-purchased) vaccines against emerging influenza pandemics. However, we note that, as discussed in [11], the benefits of responsive purchase come partly from avoiding the costs of maintaining a stockpile through non-pandemic years.

Our results suggest that the strength of the NPV depends on how early is vaccination started and the vaccine coverage level required. Specifically, we suggest that employing responsive-purchase vaccination policy that starts sufficiently early after the pandemic onset and reaches certain number of people, may be very beneficial across the influenza types resembling all past pandemics is an important finding. Considering specifically the last pandemic in the UK, the 2009 Swine flu, the outbreak was identified in April 2009, was declared as a pandemic in June 2009, peaked round July 2009 and mass immunisation started in Oct 2009 (i.e. 240 days after the start of the pandemic) [13]. Based on our findings of best-preparedness planning against this influenza (using either Figure 1(a)-(b) or Figure 2(a)-(b)), a preparedness policy of mass-immunisation based on pre-purchase vaccine is projected to have largest net-present value if the vaccination started earlier (within 84 days for low infection-severity in Figure 1(a) or 140 days in the case of high infection-severity in Figure 2(a) and covered sufficient number of people (over 60% in Figure 1(a) and over 42% in Figure 2(a). Furthermore, against this influenza strain, our results suggest that employing a responsive-purchase vaccine would have been more beneficial, and this is in line with current pandemic preparedness planning.

In this study we utilised a subset of results we had already generated using an established model [12,21] that we adapted and combined with an economic model to explore to a number of scenarios in collaboration with the Department of Health and Social Care (see [11] for details). While many combinations of the model variables can be explored using the visualisation tool we constructed, in this paper we focused on those that characterised previous pandemics. While we are aware that decisions about policies for pandemic preparedness are made in the absence of knowledge about the timing and nature of the next influenza pandemic, our work has potential to be useful if a pandemic with strains similar to the previous ones occurs in future. For example, by identifying windows of largest net-presents value of both PPV and RPV immunisation programmes in absence and presence of effective anti-viral drugs, our work can aid decision making when faced with influenza strains similar to the past ones.

Unlike other studies (e.g.[10]-[16],[17],[19]) which have focussed on evaluating a specific countermeasure against a specific pandemic, we have explored all the past pandemics of the twentieth century with different preparedness plans, accounting for the likelihood of there being a period between the point of decision and the onset of the next pandemic during which costs are still incurred. We consider that our approach is more attuned to the decisions that face policy makers and represents a direction of research that is necessary for better control of future influenza pandemics with currently unknown characteristics.

A limitation of our work compared to that of others is that, in focussing on the net-present value of mass immunisation as a lone countermeasure or as an addition to the distribution of antivirals to infected individuals, we have not sought to identify the most effective combination of countermeasures. For example, our results on the relative affordability of the pre-purchase compared to the responsive-purchase vaccine differ to those in Halder et al [19]. This could be because they include social distancing prior to mass immunisation, and the policies they evaluated incur considerable productivity losses that are not a feature of the policies we have evaluated. School closures are being actively considered as a potential measure to buy time for more severe pandemic scenarios and this will be explored in our future work.

Another potential weakness is that the model we have used is not age and risk group stratified, as we only considered mass immunisation rather than programmes that focus on

specific age/risk population cohorts and did not consider age-dependent susceptibility or case-fatality. As a consequence, the contact pattern we used is very simplistic and other deterministic (e.g. [10,11,14]) or stochastic, agent-based (e.g. [13,16,19]) models will give more realistic predictions for the spread of a pandemic within and between different population cohorts. Including age-stratified vaccine strategies is an important aspect that we will explore in future, especially in the context of evaluating the benefits of paediatric pandemic vaccination similar to the paediatric vaccination against seasonal influenza we considered in our recent work [33].

The results and the code underpinning the analysis of this work have the potential to be used in future to inform policy on pandemic preparedness and policy related to new technologies for vaccine development and production. As a range of technologies emerge for improvements in vaccine development and production, our work could prove very useful in exploring polices that involve the responsive-purchase vaccines against specific pandemics as a tool in preventing against the next pandemic.

Influenza strain	R0	Reference	CFR	References	Pandemic scenario considered as a combination of R0 and CFR
AH1N1 2009 "Swine Flu"	1.4	As median value from 57 studies reporting 78 R0 values in [41	0.025%	[34]	**Pandemic Scenario 1** (R0,CFR)=(1.4, 0.04)
			0.1%-0.9%	[35-37]	**Pandemic Scenario 2** (R0,CFR)=(1.4,0.2)
A H2N2 1957-58 "Asian Flu"	1.6	As median value from 6 studies reporting 7 R0 values in [41]	0.2%	[38]	**Pandemic Scenario 3** (R0,CFR)=(1.6,0.2)
AH3N2 1967-68 "Hong-Kong Flu"	1.8	As median value from 4 studies reporting 7 R0 values in [41]	0.2%	[38]	**Pandemic Scenario 4** (R0,CFR)=(1.8,0.2)
A H1N1 1918 "Spanish Flu"	1.8	As median value from 24 studies reporting 51 R0 values in [41]	2-3%	[39,40]	**Pandemic Scenario 5** (R0,CFR)=(1.8,2)

Table 1: Characterising the past four influenza pandemics by their transmissibility (R0) and their infection-severity (CFR) using the established literature

Parameter	Pre-purchase vaccine policy	Responsive-purchase vaccine policy
Initial susceptibility	90%	90%
RO	See Table 1	See Table 1
CFR	See Table 1	See Table 1
Vaccine efficacy	20%	60%
Vaccine shelf-life (years)	2	N/A
Probability of second wave	0.1	0.1
Weeks to achieve coverage	8 weeks	16 weeks
Effective anti-viral drugs used	Yes or no	Yes or no

Table 2: Values used at https://vaccinparamspaceanalysis.shinyapps.io/shinyPlots/ to generate simulation results presented in Figures 1-5.

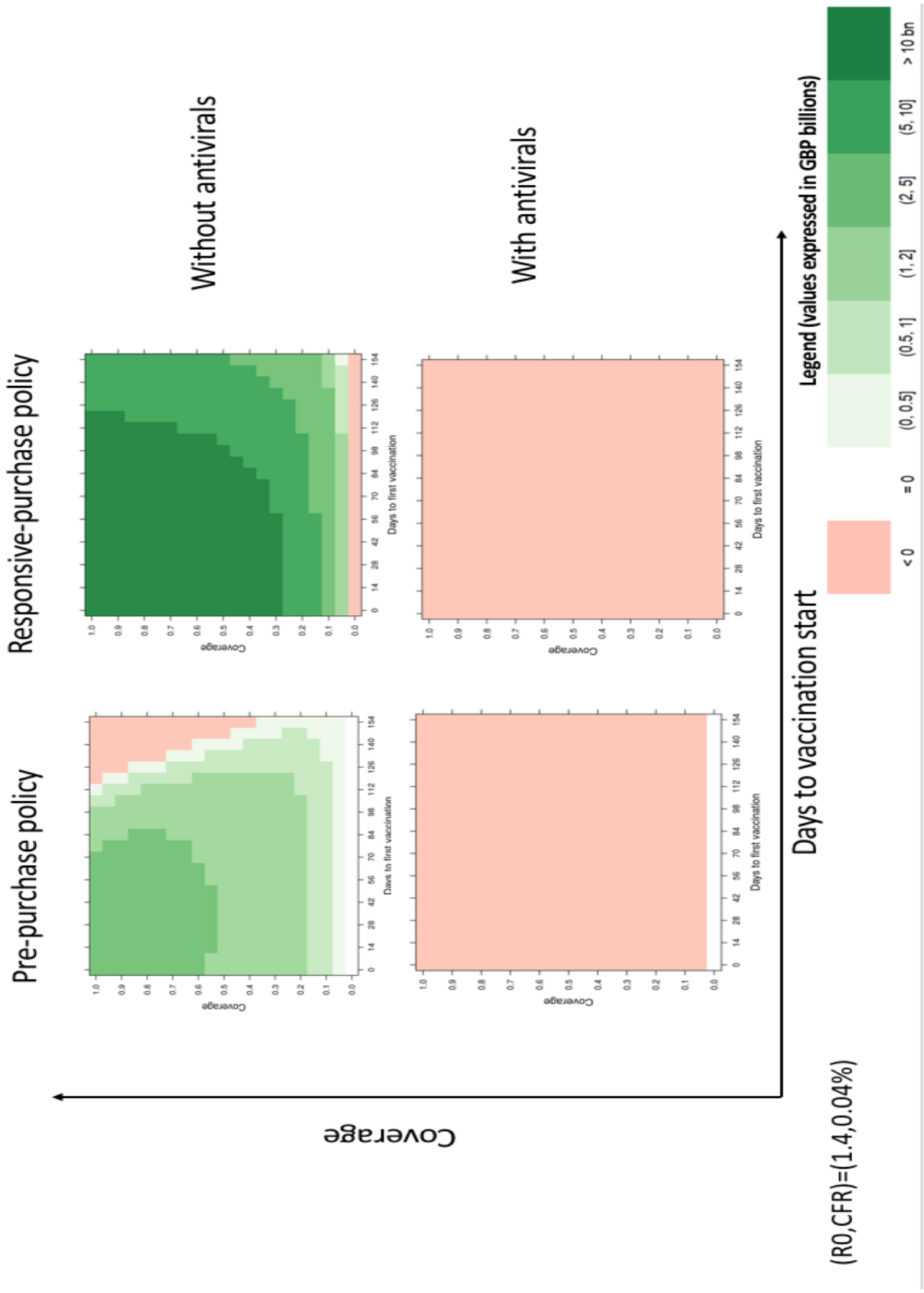

Figure 1: Simulation results for Pandemic Scenario 1 showing the net present value (NPV) of pre-purchase vaccine (PPV) and responsive-purchase vaccine (RPV) strategies in absence and presence of antivirals. The details of the modelling and economic frameworks are detailed in [11] and we use the model parameters as per Table 2 and row 2 of Table 1.

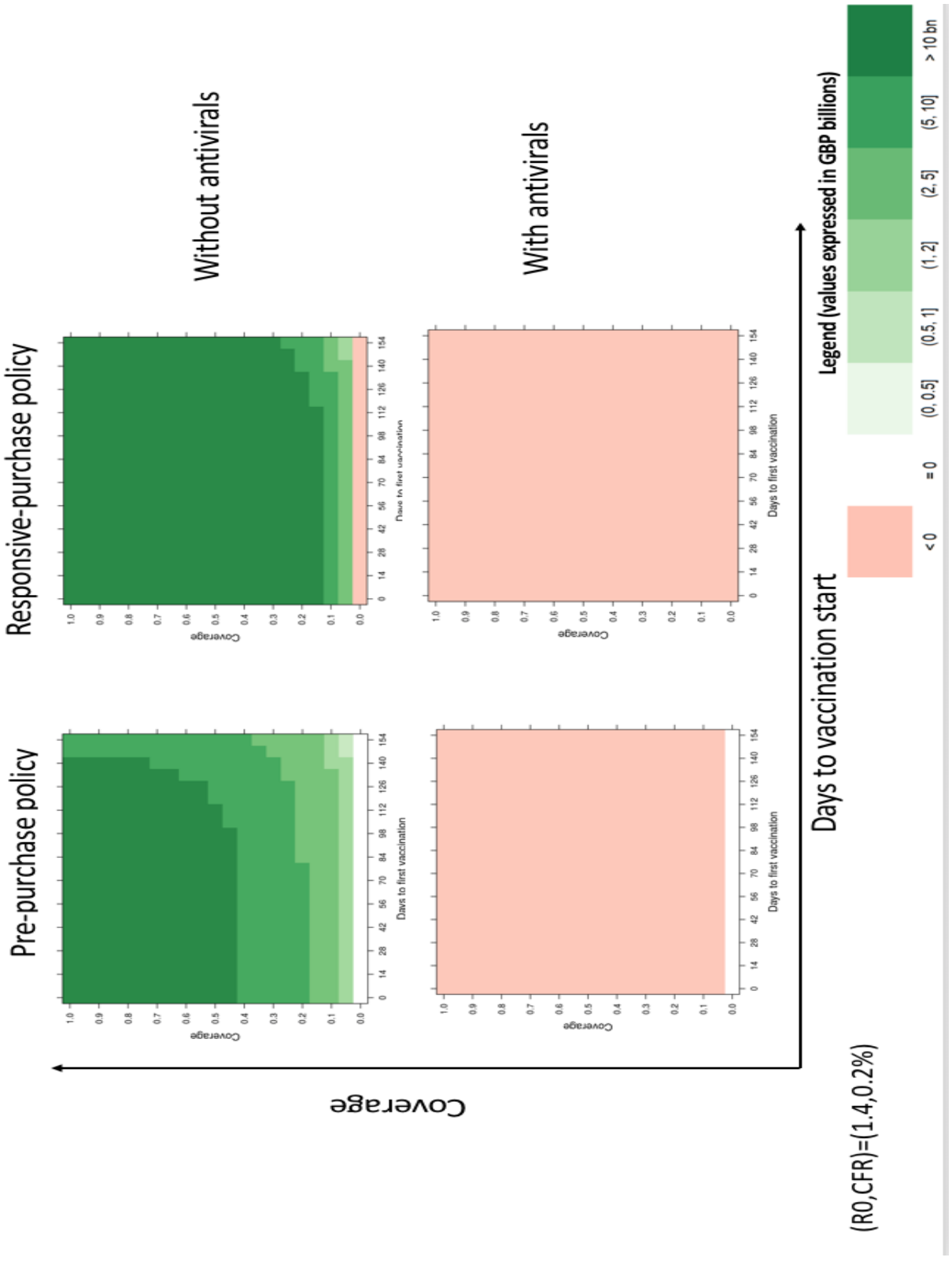

Figure 2:Simulation results for Pandemic Scenario 2 showing the net present value (NPV) of pre-purchase vaccine (PPV) and responsive-purchase vaccine (RPV) strategies in absence and presence of antivirals. The details of the modelling and economic frameworks are detailed in [11] and we use the model parameters as per Table 2 and row 2 of Table 1.

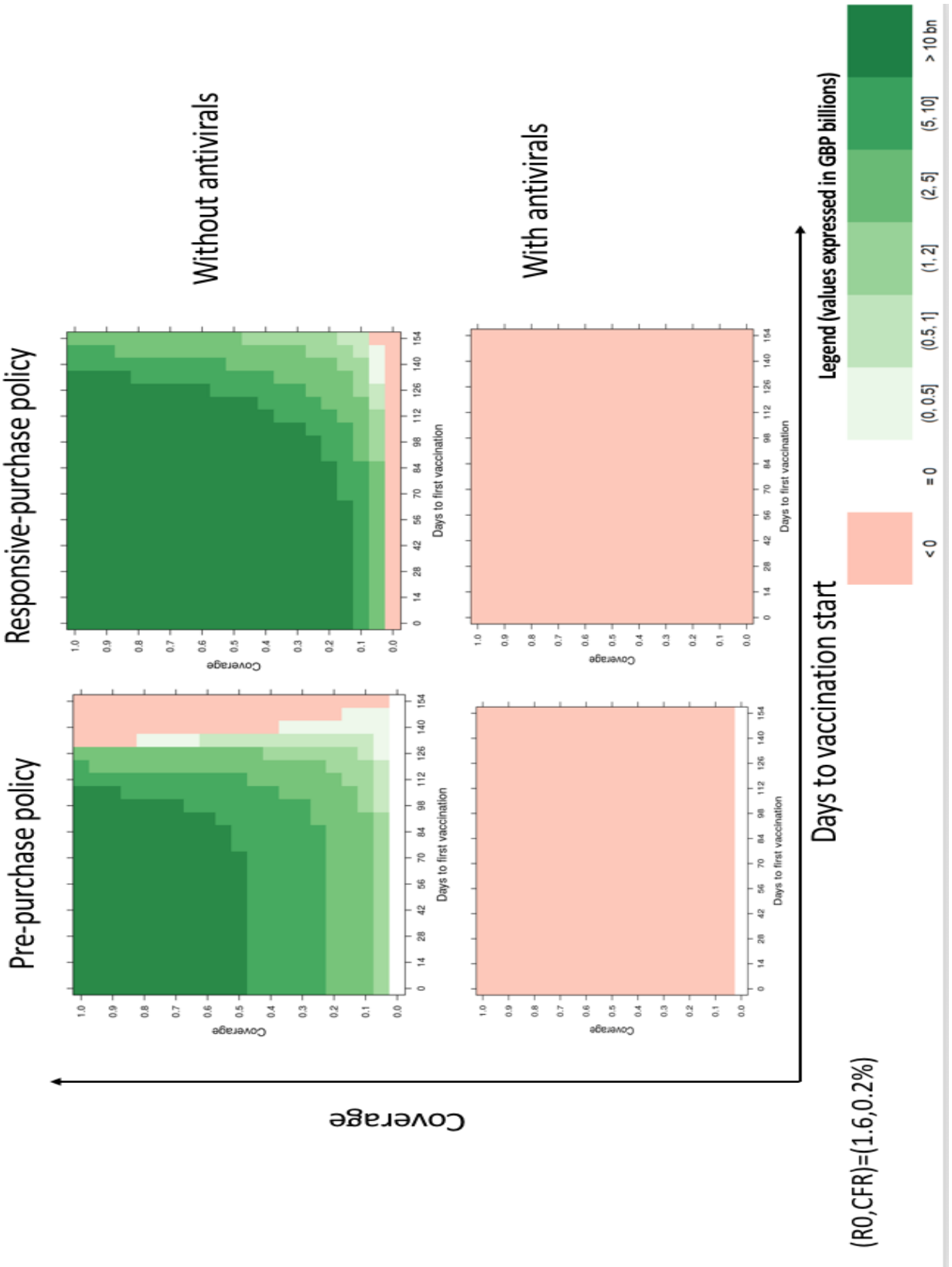

Figure 3: Simulation results for Pandemic Scenario 3 showing the net present value (NPV) of pre-purchase vaccine (PPV) and responsive-purchase vaccine (RPV) strategies in absence and presence of antivirals. The details of the modelling and economic frameworks are detailed in [11] and we use the model parameters as per Table 2 and row 3 of Table 1.

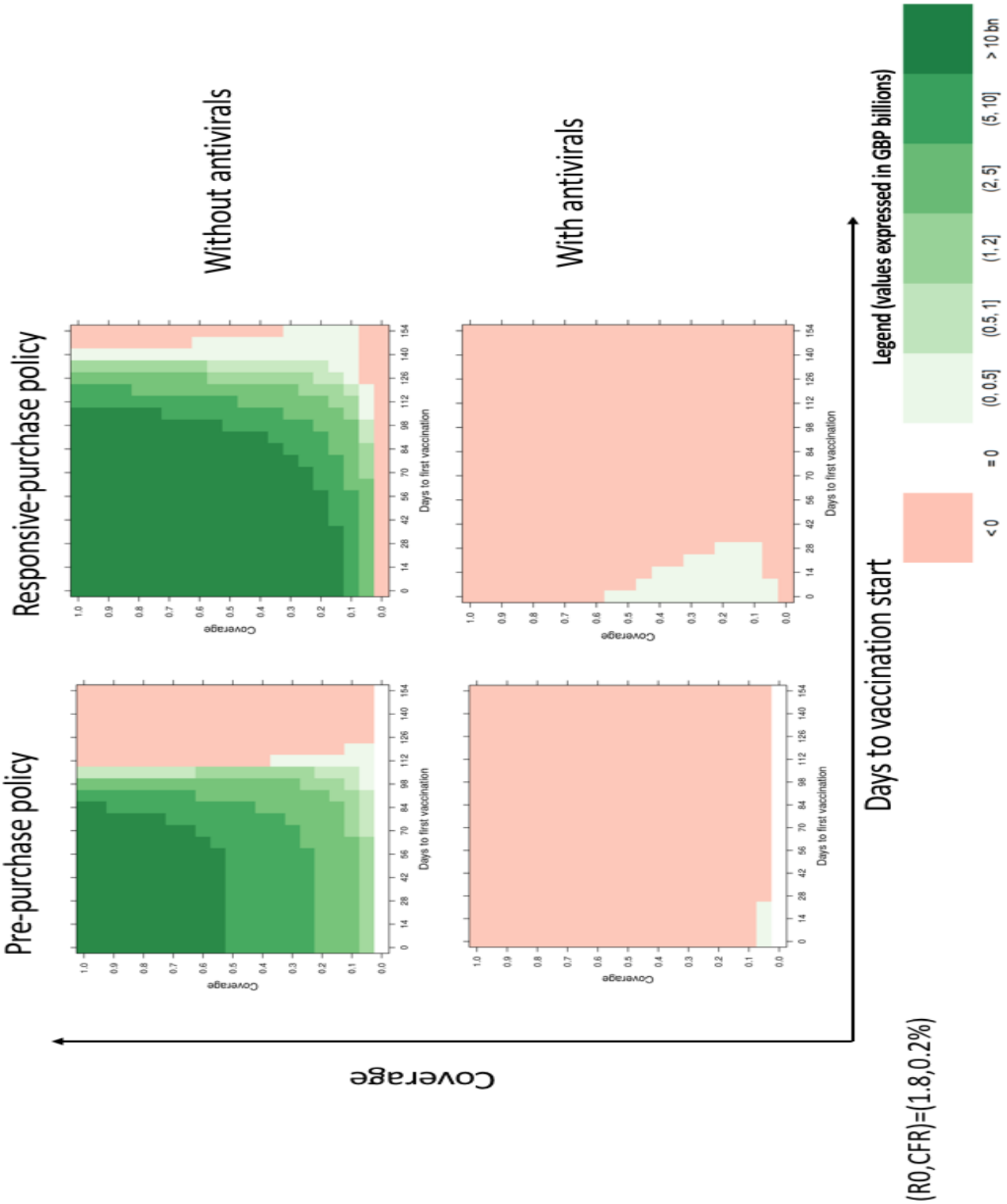

Figure 4: Simulation results for Pandemic Scenario 4 showing the net present value (NPV) of pre-purchase vaccine (PPV) and responsive-purchase vaccine (RPV) strategies in absence and presence of antivirals. The details of the modelling and economic frameworks are detailed in [11] and we use the model parameters as per Table 2 and row 4 of Table 1.

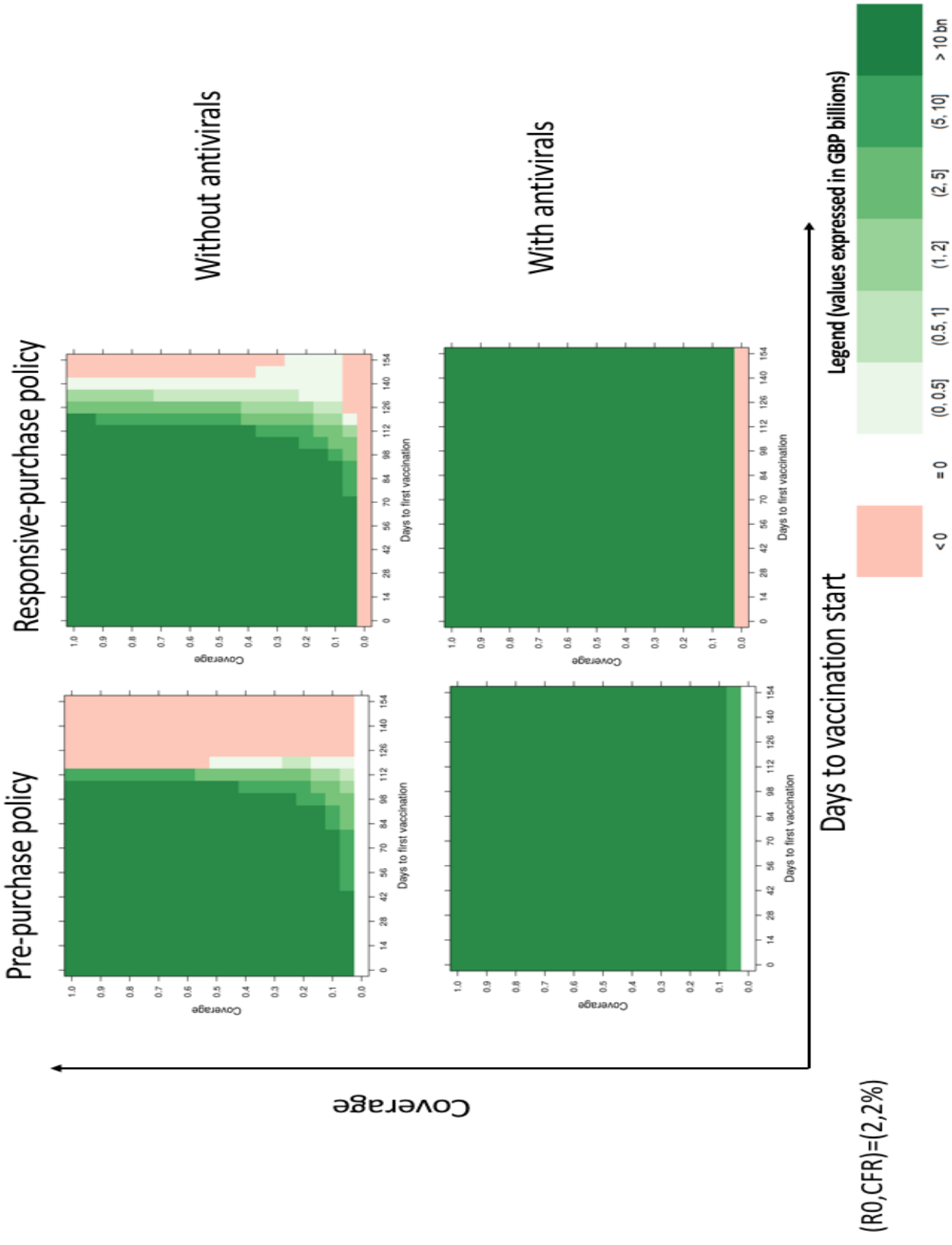

Figure 5: Simulation results for Pandemic Scenario 5 showing the net present value (NPV) of pre-purchase vaccine (PPV) and responsive-purchase vaccine (RPV) strategies in absence and presence of antivirals. The details of the modelling and economic frameworks are detailed in [11] and we use the model parameters as per Table 2 and row 5 of Table 1.

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Competing interests

All authors declare no competing interests.

Author contributions

JPG developed the work described in this paper with contributions from LG, MU, EvL, MB and RP. JPG drafted the paper with contribution from LG, MU, EvL, MB and RP and the final paper was approved by all authors.

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