Emerging from the COVID-19 pandemic: impacts of variants, vaccines, and duration of immunity

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Abstract The advent of vaccines against SARS-CoV-2 and the roll out of mass vaccination programs are thought to present the most effective means to control and even end the ongoing pandemic. However, uncertainties connected with the partial effectiveness of present vaccines, duration of immunity against SARS-CoV-2, and potential impact of variant dynamics, mean that it is still possible that the contagion could follow different future paths in different communities. Here, we use an extended SEIR for SARS-COV-2 transmission sequentially calibrated to data on cases and interventions implemented in the state of Florida to explore how these factors may interact to govern potential pandemic futures. Our data-driven forecasts indicate while the introduction of vaccinations could lead to the permanent, albeit drawn-out, ending of the pandemic if the immunity generated through vaccinations and natural infections acts over the long-term, additional futures could become possible if this immunity wanes over time. These futures will be marked by repeated waves of infection, the amplitude and periodicity of which will depend on the duration over which the immunity generated in a population will operate. We conclude that the possibility of these complex futures will require continual vigilance and perhaps fundamental changes in societal responses if we are to effectively control SARS-CoV-2.

Introduction

The steady pace of vaccine roll outs against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has raised hopes that the pandemic may soon be controlled in many economically advanced countries by as early as late 2021 or the the beginning of 2022 (***Usherwood et al.*** (***2021***); ***Young et al.*** (***2021***)). This optimism is buttressed by reported cases and hospitalizations beginning to fall in countries and settings that appear to have vaccinated the largest shares of their populations (***Chen*** (***2021***); ***Scobie et al.*** (***2021***)), and by findings that the current vaccines appear to be still protective against both infection and the development of clinical symptoms requiring hospitalizations from the currently dominant virus variants (***Polack et al.*** (***2020***); ***Cevik et al.*** (***2021***); ***Moghadas et al.*** (***2021***)). It is also becoming apparent that population immunity could be approaching herd immunity levels in many of these settings, leaving behind ever declining fractions of susceptibles available for re-igniting high intensity community outbreaks going forward (***Gumel et al.*** (***2021***)).

While the above outcomes signify that we may be approaching the endgame stage of the pandemic at least in settings that have been able to vaccinate a large fraction of their populations, several concerns still remain that may threaten the prospects of achieving a full recovery from the contagion. These include the dangers arising from the continuance of transmission among the remaining unvaccinated populations (***Milman et al.*** (***2021***); ***Vitiello et al.*** (***2021***)); uncertainties regarding the protective efficacy of individual vaccines against different virus variants, including the impacts of breakthrough infections among vaccinated individuals (***Hacisuleyman et al.*** (***2021***));

and critically the impact of a less than permanent operation of anti-viral immunity (***Altmann and Boyton*** (***2021***); ***De-Leon and Aran*** (***2021***); ***Goldberg et al.*** (***2021***)). Understanding how these factors may interact among themselves, along with changes in public observances of social mitigation measures (***Young et al.*** (***2021***)), to influence the future course of the pandemic will allow us to better determine if we are indeed on track to halting virus transmission using mass vaccinations, and hence when we may be able to achieve full recovery from the present pandemic. It will also permit assessments of whether we should expect to see another surge or indeed waves of resurgent cases going forward even in populations that have received high levels of vaccinations owing, for example, due to waning of immunity (***Getz et al.*** (***2021***)).

Understanding the impact of these interacting factors on the future course of the pandemic will thus shed light on the different paths that may be followed by the present contagion in a given setting. The elucidation and characterization of these paths will clearly also be crucial to the effective management of the pandemic going forward.

Here, we extend our previously developed data-driven socio-epidemiological SEIR-based COVID-19 model (***Newcomb et al.*** (***2020***); ***Michael and Newcomb*** (***2021***); ***Young et al.*** (***2021***)) to include vaccination and variant-specific transmission dynamics in order to investigate this issue. We use the extended model calibrated sequentially to the course of the pandemic in the state of Florida to examine the prospects of emerging from the pandemic given differential variant transmission, and the social measures and vaccinations implemented in the state. We also investigated the effects of increasing the vaccination rate and full release of social mitigation measures on the achievement of herd immunity and on the time to pandemic fade-out. Finally, we considered the outcomes that waning of immunity could have on the future behavior of the pandemic, including the dynamical impact it will have on changing immunity levels and hence on cases.

Results

Estimation of variant-specific models and path of the pandemic given long-term immunity

Figure 1a shows the course of the COVID-19 pandemic in terms of daily confirmed cases (solid lines) in Florida from early March 2020 when it first emerged to cases reported on September 22nd, 2021. These data depict the typical wave-like or cyclical trends expected for daily cases of pandemics due to public interventions and social behavioral changes (***Loeffler-Wirth et al.*** (***2020***); ***Cacciapaglia et al.*** (***2021***)). It also shows the wave-like advent and spread of SARS-CoV-2 variants with the alpha variant first emerging in late December 2020 and the delta variant first appearing in June 2021 before becoming the pre-dominant variant from mid-July 2021 to date. The dotted lines in the figure portray the median predictions of our data-driven variant-extended COVID-19 best-fitting ensemble model. These indicate the ability of our data-driven system to faithfully capture the changing dynamics of these viral variants, including the overtaking of the alpha variant by the more transmissible delta variant (estimated rate of transmission being 1.8 for the delta variant compared to 1.1 and 1.2 for the alpha and original variants respectively during the 4rd wave (Figure 1a)).

The long-term forecasts of COVID-19 daily cases (to end of 2022) arising from all variants combined are shown in Figure 1b for future scenarios varying in changes to levels of implemented social protective measures and vaccinations. The latest (and largest) wave of pandemic peaked on August 26th 2021 with 22,400 median daily cases in line with case reports (Table 1), with cases declining thereafter under current levels of social mitigation (23%) and vaccinations (20,000/day) (see data in Supplementary Material). Under the default expectation that immunity to SARS-CoV-2 is long-term, the predictions for this scenario indicate that the pandemic will fade out early 2022 (see below). The blue solid and dashed curves show the impact of fully releasing social protection measures (but at current vaccination rate); the results show that such a full release from September 23rd 2021 will result in only a small increase in cases (over those produced under maintaining

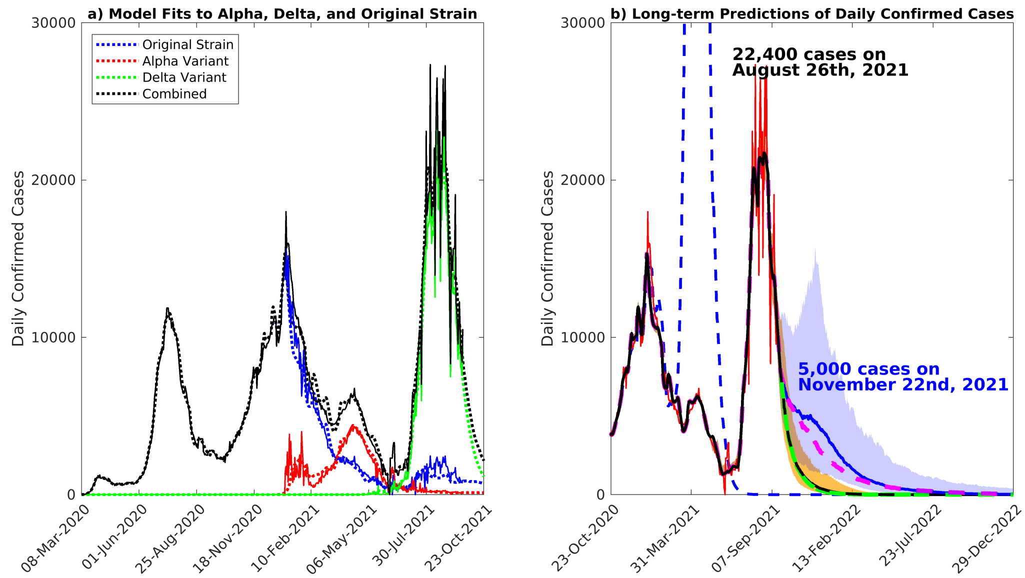

Figure 1. a) Median model fits to the 7-day moving average of daily confirmed case data, along with short-term predictions. The cases due to the alpha, delta, and other variants are given in red, green, and blue, respectively. b) Long-term forecasts of daily confirmed cases until the end of 2022.The 7-day moving average of confirmed case data is given in red. The median model predictions given current social distancing measures and vaccination rate are given by the black curve, while the model predictions given a full release of social distancing measures are given by the blue curve. The yellow and blue shading represent the 90% confidence intervals for these two scenarios. If the current vaccination rate is increased by 1.5x, the median model prediction given current social distancing measures is given by the green dashed curve, while in the case of full release of social measures, it is given in magenta. The blue dashed line represents a full release of social measures on Mar 1st, 2021, when the fraction of immunity was much lower than present.

current social protective measures) which will then decline to small levels from July 2022 (blue solid curve). By contrast, if social mitigation measures had been released on Mar 1st 2021, a major spike in cases would have occurred (blue dashed curve). Increasing the current vaccination rate 1.5x (to approximately mimic the upcoming school vaccinations) under maintenance of present social protective measures will result in lower cases in the future but not significantly so compared to the predictions for the pandemic future given continuance with current social measure/vaccination levels (green dashed curve). Releasing the current social mitigation measures fully while increasing the current vaccination rate by 1.5x, however, will result in an increase in cases but this increase will only be slightly lower than that predicted for when the current vaccination rate is continued (dashed magenta curve and Table 1). These results indicate that releasing social measures fully and increasing the vaccination rate going forward will have only a moderate impact on the future declining course of the pandemic under conditions of permanent immunity.

These results highlight the impact of the changed immunity landscape in Florida, where currently we predict that 84% of the population have developed immunity to the virus from both infection and vaccination (Fig. 2a), with herd immunity (estimated at 91%) expected to be reached as early as November 22nd 2021. The fraction of the population immune was much lower in March 2021 (approximately just 30-35%), and thus forms the primary reason for the large spike in cases predicted for a full release of social measures at that stage compared to the small increase in cases resulting from the release of these measures (and increase in vaccinations) going forward. Interestingly, Figure 2b shows that currently vaccinations have contributed to 53%, while naturally acquired immunity (ie immunity through infection) comprise 33% of the population immunity generated against SARS-CoV-2 thus far in the population.

The forecasts of the models updated using data to September 22nd 2021 for the mix of social measures/vaccination levels investigated for hospitalizations and deaths are also shown in Figure 3

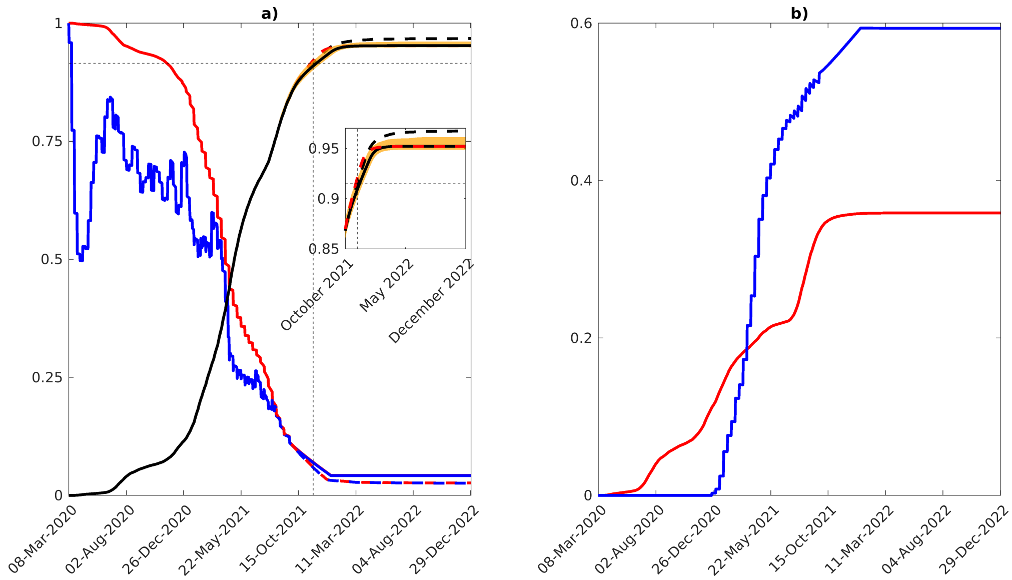

Figure 2. Changes in the proportions susceptible and immune to SARS-Cov-2 from March 2020 to present in Florida. a) Total proportion susceptible(red), proportion that is effectively susceptible due to mobility restriction (blue), and total immune (black) over time. The proportion immune given current social measures and vaccination is given by the solid black line, while a full release of social measures is shown as a dashed black line. If the vaccination rate is increased by 1.5x, the proportion immune is represented by the red dashed line. The 90% confidence interval is shown as a yellow band. As of September 22nd 2021, 11% of the population were susceptible, while 84% were immune.If social measures are released, 91% of the population will have immunity on November 27th, 2021, the date at which cases will fade-out given a full release of social measures. This level of immunity(91%)is achieved on November 30th if current social measures are continued and achieved on November 15th if the vaccination rate is increased by 1.5x. b) Proportion of the population with natural immunity (red) along with the proportion of the population with vaccine-conferred immunity (blue). As of September 22nd 2021, the fraction of the population with natural immunity is 33%, while the fraction with vaccine-induced immunity is 53%.

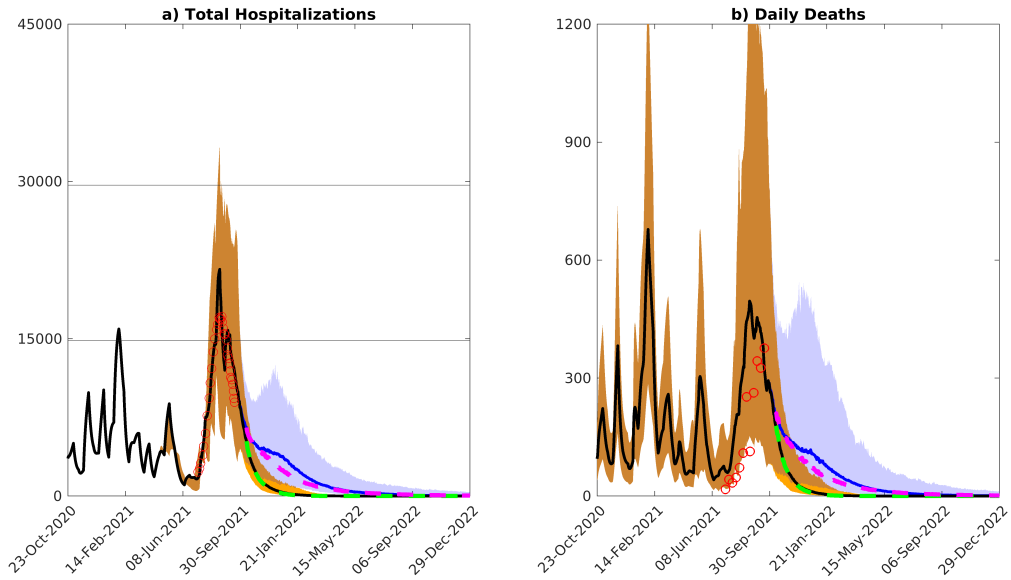

Figure 3. Median predictions of a) total hospitalizations and b) daily deaths over time. Several scenarios are shown. Median model predictions given current social distancing measures and current vaccination rate are shown by the solid black curve, while the median model predictions given a full release of social measures is shown in blue. The 90% confidence interval for these two scenarios (current social measures and full release of social measures) are given by the yellow and blue bands, respectively. If vaccination rate is increased by a factor of 1.5x, the median model predictions are shown by the green dashed curve in the case of current social measures and shown by the magenta dashed curve under a full release of social measures. The daily hospitalization and death data is shown by the red circles.

and Table 1. The results corroborate the findings for daily confirmed cases in that while no peaks will be seen or emerge for the scenarios that maintain current social measures into the future irrespective of vaccination rate, whether followed at the current rate (20,000 doses per day) or 1.5x the current rate, new small-sized peaks will develop in the future (in November 2021) for the two scenarios in which social measures are fully released going forward (Table 1; Figure 3).

Table 1. Peak Cases, Hospitalizations, and Deaths

Scenario		Cases	Hospitalizations	Deaths
With Sustained Long-Term Immunity				
Current social measures	Current vaccination rate	No Peak	No Peak	No Peak
Current social measures	1.5x vaccination rate	No Peak	No Peak	No Peak
Full release of social measures	Current vaccination rate	5,000 cases on November 22nd, 2021	4,000 beds on October 8th, 2021	110 deaths on October 10th, 2021
Full release of social measures	1.5x vaccination rate	3,200 cases on November 22nd, 2021	3,100 beds on October 8th, 2021	85 deaths on October 10th, 2021
With Waning of Immunity over 1yr				
Current social measures	Current vaccination rate	18,000 cases on May 20th, 2022	16,500 beds on July 26th, 2022	480 deaths on July 22nd, 2022
Current social measures	1.5x vaccination rate	23,000 cases on May 22nd, 2022	19,000 beds on June 13th, 2022	580 deaths on June 23rd, 2022
Full release of social measures	Current vaccination rate	56,000 cases on November 26th, 2021	48,400 beds on December 4th, 2021	1,400 deaths on December 11th, 2021
With Waning of Immunity over 2.5yrs				
Current social measures	Current vaccination rate	10,700 cases on November 25th, 2022	9,700 beds on December 3rd, 2022	320 deaths on December 17th, 2022
Current social measures	1.5x vaccination rate	11,800 cases on September 30th, 2022	10,000 beds on November 3rd, 2022	350 deaths on November 15th, 2022
Full release of social measures	Current vaccination rate	24,700 cases on December 4th, 2021	21,000 beds on December 9th, 2021	700 deaths on December 23rd, 2021
With Waning of Immunity over 5yrs				
Current social measures	Current vaccination rate	No Peak	No Peak	No Peak
Current social measures	1.5x vaccination rate	No Peak	No Peak	No Peak
Full release of social measures	Current vaccination rate	9,900 cases on November 22nd, 2021	9,100 beds on November 25th, 2021	270 deaths on December 17th, 2021

The impact of increasing vaccinations by 1.5x the current rate will have only a small effect on these predicted peaks. Note although increases in these clinical outcomes are predicted in the future for these scenarios, the daily numbers at peak will be substantially lower than those which occurred (and predicted) in August 2021 for the base scenario investigated, viz in which social measures and vaccinations are held at their current estimated levels.

Pandemic fade-out probabilities under long-term immunity

We used projections from individual models belonging to our best fitting multi-model ensemble to calculate the probability of pandemic fade-out (see Methods). Figure 4a shows that if current social measures and vaccination rates are maintained, then we will reach very high probability of fade out (>99%) of the pandemic by January 2nd, 2022. However, releasing all social measures going forward will delay the time to achieving the fade out of the pandemic (Figure 4b). The results show that under this scenario, fade out at the corresponding 99% probability level will now only occur just after December 1st 2022. However, it is important to note that if all social measures are fully released, the range in predicted cases will begin to diminish significantly from July 1st 2022 onwards, with the 90% confidence interval of cases ranging from 10-1,200 cases on that date to just between 0-400 cases after January 1st 2023. Thus, even though the probability of resurgence will remain high (as high as 60% on July 1st 2022) until end of 2022 (around 10%), the size of any resurgence during this period is likely to be very small and well within the management capacities of hospitals in Florida. The red curve in Figure 4b shows the corresponding probability of cases remaining below 1,200 (the peak size of the first wave (Figure 1)), and highlights that if this threshold (rather than 0 cases) is followed then a very high probability for the safe containment of the pandemic (>99%) will be reached in the state by August 2022.

Finally, if the vaccination rate is raised from its current level of 20,000 doses per day to 30,000 doses per day (a 1.5x increase), the pandemic fade-out will be achieved on February 15th 2022 if current social measures are maintained, and December 1st, 2022 in the case of full release. These results indicate that, counterintuitively, increasing vaccination by 1.5x the current rate will result in a delayed fade-out of the pandemic under conditions of permanent immunity. This is primarily because of the generation of higher breakthrough infection cases with higher rates of vaccinations.

Future dynamics under waning immunity scenarios

Figure 5 illustrates the likely paths of the pandemic if population immunity is not permanent or long-term and were to wane over durations of 1 year (fast waning), 2.5 years (moderate waning) to 5 years (semi-permanent). Forecasts are shown for the situation in which current social protective measures and vaccination rates are continued in the future and when social measures are fully released from September 23rd 2021 onwards. We also show results for increasing the vaccination rate by 1.5x the current rate, while maintaining current social measures into the future. It is immediately apparent as expected that if immunity were to wane, the pandemic will settle into a cyclical pattern of rise and decline in cases with amplitudes (and peak cases) and inter-wave periods dictated by the duration over which immunity wanes. Sizes of the oscillating waves will decline while lengths of inter-wave periods will increase with increasing duration of immunity (Figure 5). If the current social measures/vaccination rate scenario was to be maintained, however, the pandemic will decline and remain suppressed for a long period of time and any resurgence (beyond the period of simulation shown) will be easily containable. Full release of social measures, by contrast, can still be dangerous and could result in large resurgences in cases particularly if duration of immunity is short (eg. 1 or 2.5 years). The predicted peak cases, hospitalizations and deaths given in Table 1 for these two scenarios (ie. continuing current vaccination rate with current social measures versus full release of social measures) further buttress this conclusion. Increasing the vaccination rate, compared to maintaining the current rate, will initially cause a decrease in daily confirmed cases, but will lead to a small peak above the cases forecasted for continuing with the current rate. This occurs only if immunity wanes quickly (over 1 year, Figure 5). However, the cu-

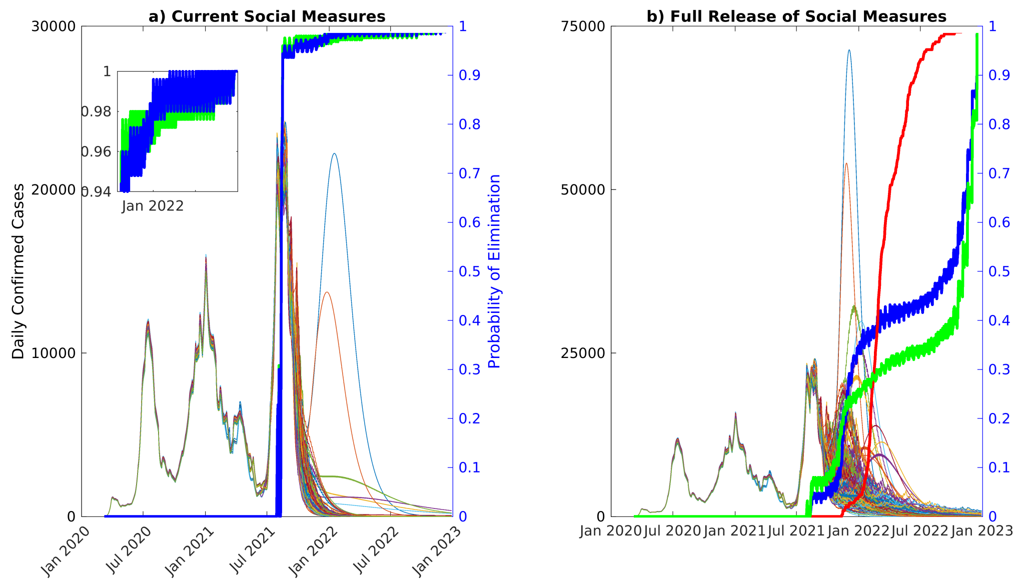

Figure 4. Ensemble of predictions of daily confirmed cases, and probability of elimination over time, given a) current social measures and b) after the full release of social measures. The predictions of individual models (250 in total, see Methods) from the best-fitting model ensemble are presented by the thin curves in the background of the figure. For the current social measures and vaccination rate, the probability of fade-out is given by the blue curves, whereas increasing vaccination to 1.5x is presented by the green curves, respectively. The probability that the cases remain lower than 1,200 (the size of the first wave peak) is given by the red curve. If current social measures are continued along with the current vaccination rate, 99% probability of elimination will be achieved on January 2nd 2022, while if social measures are fully released, 99% probability of elimination will be achieved on December 1st, 2022. With a 1.5x increase in vaccination, the corresponding 99% probability of pandemic fade-out will be achieved on February 15th 2022 and December 1st, 2022 for continuing with current social measures and given a release of social measures, respectively. Even though there is a significant probability of resurgence given a full release of social measures, the size of the wave is likely to be very small. After July 2022, the probability of a resurgence causing more than 1,200 peak daily cases is less than 5%.

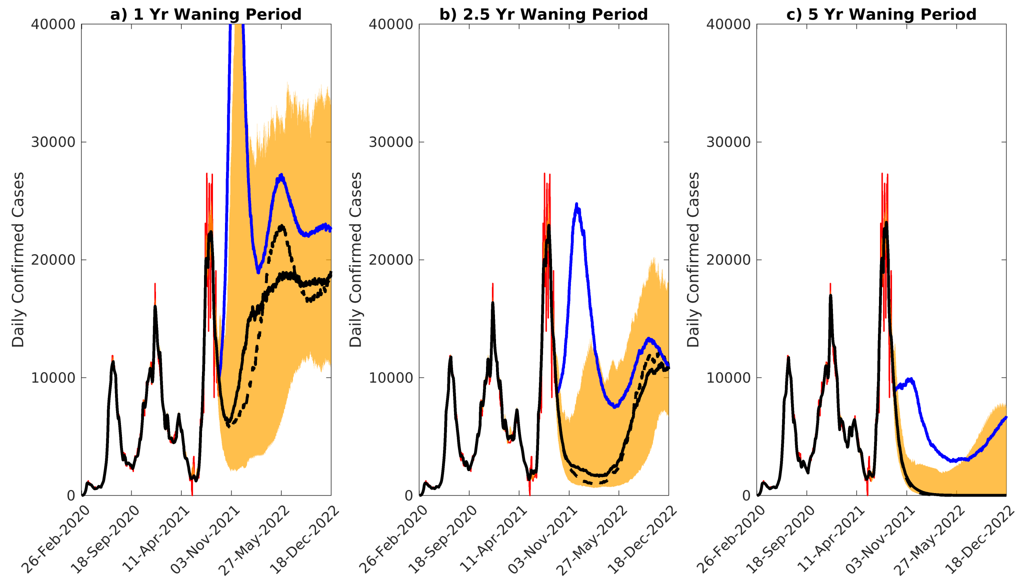

Figure 5. Scenarios of waning immunity, given waning intervals of 1 year, 2.5 years, and 5 years. The median model predictions of confirmed cases given current social distancing measures and release of social measures are given by the black and blue curves, respectively. The 90% confidence interval for the median case is given by the orange shading, while the confirmed case data is given in red. The dashed black curve shows the course of the pandemic given a 1.5x increase in daily vaccination rate, while maintaining the current social measures in Florida.

mulative cases generated are reduced by increasing the vaccination rate (see Appendix 1, Figure 4), indicating that the increase in daily cases is a transient outcome of infection breakthroughs among the vaccinated individuals particularly when waning of immunity is rapid. Figure 6 clarifies the primary reasons for the oscillatory dynamics forecasted for the pandemic under conditions of waning immunity (as depicted in Figure 5); the results show that with waning of immunity, herd immunity may never be reached leading to revivals of the susceptible fraction in the population with the negative impact on achieving population immunity and the increase of susceptibles more apparent as the duration of immunity declines.

We calculated and used the RMSE values of fits of our models to the case data observed over a 4-week period around the peak of the 4th wave as a means to detect signals for the emergence and operation of waning immunity. In this approach, we considered that better fits by models with waning immunity over the model with permanent immunity would allow us to distinguish which of these types of immunity may be becoming operational, and thereby offer a clue as to the likely future path that might be followed by the pandemic in Florida. Table 2 displays the RMSE values and relative errors of the fits of the models without and with waning of immunity. These show that models with waning immunity provided better fits (smaller RMSE values) and reduced the model errors more relative to the model with no waning of immunity. However, the model that gave the best fit and reduced modelling errors most was that which incorporated the longest wanning duration (5 years) investigated in this study, indicating that if waning of immunity is playing a role in describing the current state of the pandemic then the future path of the pandemic will follow one in which immunity may act over a relatively long duration (eg. the path of the pandemic arising from immunity that wanes over 5 years (Figure 4)).

Discussion

While there are understandable expectations among both the public and governments that vaccinations may finally portend the end of the COVID-19 pandemic, our data-driven modelling results reported here show that the pandemic could in fact follow different future paths depending on

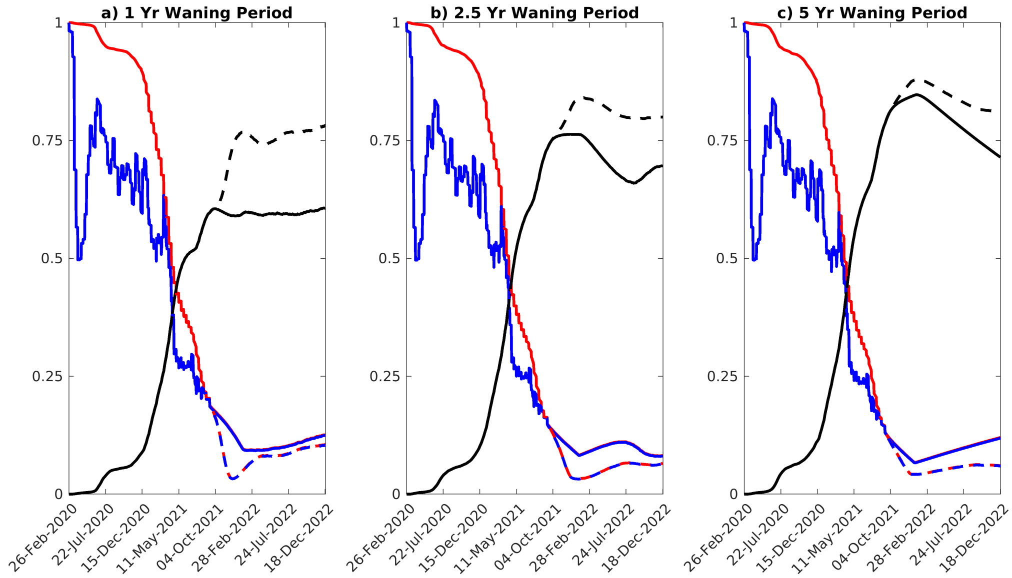

Figure 6. Scenarios for achieving herd immunity, given waning of immunity. Forecasts for total proportion susceptible (red), proportion that is effectively susceptible due to mobility restriction (blue), and total immune (black) are shown over time. Solid curves represent the impact of maintaining current social measures and vaccination rates, while the dashed curve denotes the effects for a full release of social measures.

Table 2. RMSE and relative error of models with and without waning of immunity, from July 17th, 2021 to Aug 17th, 2021 (4th wave peak).

	RMSE	Relative Error
No Waning	55.3	0
1yr Waning	51.0	-4.3%
2.5yr Waning	47.9	-10.1%
5yr Waning	46.7	-12.4%

how rates of vaccinations may interact with variants, levels of social mitigation measures followed by a community, and critically on the effectiveness and durations of the immunity generated by the current vaccines in a population. Our simulations of the impacts of these variables generated for the course of the pandemic in Florida indicate that such COVID-19 futures may range from a protracted decay of cases to eventual fade out of transmission to a situation in which the pandemic will demonstrate oscillatory dynamics for the foreseeable future. These results suggest that contrary to popular belief there is a continued need to be vigilant and to respond appropriately to signals from evolving data that will allow distinction of which of these paths may arise and play out in different populations.

It is clear that if the population immunity to SARS-Cov-2 generated by vaccinations and from infections that have occurred in Florida operates over the long-term, then one future for the pandemic in the state with continuation of current levels of vaccination and social distancing measures is to decay steadily until the pandemic fades out or ends with a high probability (Figure 4). Indeed, if a 99% fade out probability is used, we estimate that this will occur around December 21st 2021. We also show that under such long-term immunity, a full release of social measures from September 23rd 2021, irrespective of whether vaccinations are maintained at the current rate or increased 1.5x (Figure 1), will no longer result in large increases in cases as would be the case if such a release had occurred earlier in 2021 (March 2021). Increasing the vaccination rate to 1.5x while maintaining the current social measures into the future will also have only a little impact on this declining future path of the pandemic under the same circumstance in which the evolved immunity acts over the long-term (Figure 1). Essentially, these outcome patterns are also forecasted for hospitalizations and deaths (Figure 3 and Table 1), with only small increases in these outcomes predicted for a full release of the currently observed social measures irrespective of increased (1.5x) or whether the current vaccination rate is followed into the future.

These results indicate that if immunity acts over the long-term and provided that the current vaccination rate is continued into the near-medium future, then it might be possible to emerge relatively safely from the pandemic in Florida going forward even with the immediate dropping of all social activities. The primary reason for this optimistic prognosis can be gleaned from Figure 2, which shows the rates by which population-level immunity has evolved in the state. Our results indicate that, currently, 86% of the population of Florida may have already developed immunity to the virus, with vaccinations contributing to 53% and naturally acquired immunity from infections contributing to the rest (33%) of the level of immunity currently predicted to be operational in the state. As can be seen from the figure, such a high level of immunity not only corresponds to a steady shrinking of the fraction of people still susceptible to the virus (currently we estimate this to be around just 11% of the population), but it is also significantly near the 91% herd immunity level required to reduce the transmission of the virus until fade out of the pandemic occurs. We forecast that Florida will likely achieve this immunity around November 30th 2021 with the continuation of current vaccination/social measures levels, further supporting the optimistic expectation that the state may be able to emerge safely soon from the pandemic under these conditions. Note that neither increasing the vaccination rate, for example by vaccinating school-age children (***Gostin et al.*** (***2021***); ***McLaws*** (***2021***); ***Schleiss et al.*** (***2021***)), or fully releasing social measures will have a major in affecting the date by which herd immunity in Florida will be attained (Figure 2); again, this is due to the fact that the currently accomplished immunity level in the state is now very close (just 5% points away) from herd immunity.

While the above results would suggest that it might be safe to re-open the state of Florida fully if the high level of population immunity attained thus far in the state acts over a long-term, it is apparent that full release of all social mitigation measures and increasing vaccination rates further, while not impacting case numbers or the date of achieving herd immunity significantly, can have contrasting effects on the achievement of the eventual fade-out of the pandemic (Figure 4). Thus, our forecasts show that fully releasing the level of social measures observed by the public to September 22nd 2021 will significantly lengthen the time to when the current pandemic will fade out at high (99%) probability (up to a year later, viz. December 1st 2022) than if current social measures and vaccination rates are maintained (with fade out at this probability occurring on December 21st 2021). This drawing out of the tail of the pandemic can carry substantial continued potential for the resurgence of the pandemic (from a resurgence risk as high as 60% on July 1st 2022) until eventual fade out is predicted for the end of the coming year. This is because such long pandemic tails, while unlikely to result in large-size resurgences (Figure 1 and Figure 4), can produce conditions in which very extreme and risky outcomes with non-negligible probabilities, eg. emergence and spread of more contagious and possibly more immune evasive mutants (***Otto et al.*** (***2021***); ***Pucci and Rooman*** (***2021***)), can arise to dramatically change the future of the pandemic. This implies while as we show that it might be possible to contain the pandemic earlier by tolerating a level of cases that might not lead to substantial disease or mortality (eg. the 1,200 cases we used in the fade out calculations shown in Figure 4), such containment apart from having to continue with control measures (eg. continue with either current social protective measures or vaccination rates) to ensure that cases do not rise back up above set thresholds, will still carry significant heavy tail risks that will eventually confound currently applied control methods (***Flyvbjerg*** (***2020***)).

We indicate that one way to cut the long tail of the pandemic is to increase vaccination rates such that we may achieve fade outs of the contagion earlier (Figure 4). Thus, while we show that increasing vaccinations may not allow achieving permanent herd immunity significantly earlier than continuing with the current vaccination rate and level of social measures in Florida (Figure 3), efforts to increase the delivery of this intervention will allow hastening the end of the pandemic (Figure 4). In this respect, our results support the current focus on administering vaccines to school-aged children as soon as possible. Not only will such efforts shrink the pool of the remaining important group of susceptibles in the population quickly, but it will also significantly reduce the impact of superspreading events (very likely to occur in school settings for example) that have been shown to play an important role in the generation and maintenance of persistent heavy tails in the case of COVID-19 (***Conte et al.*** (***2021***)).

Our projections for the course of the pandemic if immunity were to wane, however, indicates that while we can expect eventual fade-outs of the contagion in Florida, as discussed above, if the immunity generated from vaccinations and natural infections is permanent, any waning of this immunity can result in dramatically different future paths for SARS-CoV-2 transmission (Figure 5). Such a future will be complex but essentially the pandemic dynamics will be characterized by damped oscillations or formation of repeat waves of infection with the size of repeat infections and the inter-wave periods or periodicity of the oscillations depending on how fast immunity wanes (***Heffernan and Keeling*** (***2009***); ***Giannitsarou et al.*** (***2020***); ***Good and Hawkes*** (***2020***)). Faster waning could lead to sizeable infection waves and shorter inter-wave periods into the future, but over the long-run the pandemic will shrink in size and tend towards an endemic steady state (Figure 5). Our simulations further indicate that these effects will be accentuated if all social protective measures are fully released at current vaccination rates, but that if the current social measures alongside present vaccinations are continued then it is possible to not only curb peaks of the repeat waves but also lengthen the inter-wave period. If immunity were to wane over a relatively long period of time (5 years in our simulations), then the later interventions could even be optimal in curbing the oscillatory dynamics significantly to allow practical control of the pandemic (Figure 5).

At the time of writing, it is still not clear how long immunity to SARS-CoV-2 lasts although it is becoming apparent that immunity is likely to wane (***Altmann and Boyton*** (***2021***); ***De-Leon and Aran*** (***2021***); ***Goldberg et al.*** (***2021***)). However, as shown in Table 2, the best fit to the August 2021 peak cases observed in Florida in our simulations is provided by the model characterized by a moderately-long (5 years) duration of immunity, indirectly supporting the above findings from empirical studies that the overall population-level immunity (from both vaccinations and natural infections) generated to SARS-CoV-2 is likely to wane but at a rate that may not cause too rapid a decline in the achieved immunity. There is also growing evidence, in this connection, that the effectiveness (and duration) of immunity from vaccinations may differ from that induced by natural infections (***Gazit et al.*** (***2021***)). Such differences, if true, could indeed be driving the present post-vaccination resurgence in cases observed for US states that have achieved the highest vaccination rates relative to those that are yet to attain such levels, such as Vermont (https://www.nytimes.com/interactive/2021/us/vermont-covid-cases.html). We contemplate future work addressing these differences for the course of the pandemic, including assessing the optimal strategy (eg. introduction of 3rd booster vaccinations with or without minimal social mitigation measures (***Altmann and Boyton*** (***2021***)) for curbing any detected oscillatory dynamics in the transmission of the virus in different control settings. Note that these impacts of waning immunity could in reality also mean that policy makers might need to consider tuning and instituting repeat measures, including retaining some of the least socially disruptive social measures, to prevent the repeated flare-ups of the pandemic over a foreseeable future until some steady endemic state in viral transmission is reached. Such permanency in responses may be seen as representing a new post-pandemic normal as it essentially involves fundamental longer-term changes to how a society functions normally such that viral transmission over the near-term future is contained within levels that may be safely tolerated (***Rypdal*** (***2021***)).

We have largely focused on the dynamics of infections in this study, although we show that if immunity is permanent, both hospitalizations and deaths will decline in the future under current vaccination and social mitigation rates (Figure 3). A full release of social measures will result in an increase in both variables slightly in the immediate future after which both will again tend to fade alongside infections. While we could expect both variables to increase perhaps significantly above current levels if immunity were to wane rapidly as a result of the evolution of large repeat infection waves (Figure 5), recent data suggests that mortality rates may be declining in relation to infection levels overall owning to clinical as well as improvements in hospital care, increased testing, roll out of vaccinations, and possibly due to reduction in infective doses of the virus (***Boudourakis and Uppal*** (***2021***); ***Hasan et al.*** (***2021***)). This decoupling of deaths/hospitalizations from infection cases raises another possible future post-pandemic normal, viz. that societies could learn to live with a controlled level of transmission going forward via both the use of repeat vaccinations and the use of newly emerging therapeutics for managing disease outcomes (***Rypdal*** (***2021***)). In this scenario, long or fat-tailed risks could be managed by targeting control (via temporary social distancing measures and/or targeting vaccinations to unvaccinated individuals) to emerging high-risk settings or sub-groups. Such post-pandemic normal strategies, however, will require implementing strong spatially explicit surveillance systems for tracking emerging cases as well as variants, and evolving adaptive management structures and capacities within health systems (***Getz et al.*** (***2021***)), which may be possible in settings with advanced, well-resourced, public care institutions but may prove challenging for less developed populations.

In summary, our data-driven forecasts for the future course of SARS-Cov-2 in Florida indicate that contrary to the expectation that the introduction of vaccinations could lead to the permanent ending of the pandemic, additional futures could become possible if the immunity engendered through vaccinations and natural infections wane over time. Such futures will be marked by repeated waves of infection, the amplitude and periodicity of which will depend on the duration over which the generated immunity in a population will operate. These complex futures will require recognition that continual vigilance and perhaps fundamental longer-term changes over the foreseeable future in both governmental responses and societal functioning as part of a new post-pandemic normal will be needed to control and mitigate against continuing outbreaks. A key current unknown that may confound these conclusions, however, is the period over which immunity to SARS-Cov-2 lasts (***Altmann and Boyton*** (***2021***); ***De-Leon and Aran*** (***2021***); ***Goldberg et al.*** (***2021***)). Large repeat waves with short periodicity are possible with rapid waning of immunity, which will require strong control measures. We may be observing this already in US states, such as Vermont, that are observing large post-vaccination resurgence in cases despite high levels of vaccination. Another limitation of our work is that we use best-fitted models to project outcomes of various scenarios into the future. While such projections provide insights to possible future behaviors of the pandemic, it does not capture non-constant changes in future parameters related to interventions or virus transmission (***Jung et al.*** (***2020***); ***Kochańczyk et al.*** (***2020***)). Nor does it capture the reality that responses by policy-makers are often to the present incidence rate, which are likely to significantly influence the future course of the pandemic in complex ways (***Adiga et al.*** (***2020***)). Our data-driven projections are also dependent on the quality of data used to calibrate the present model through time. Anomalies in the data could bias model parameters and hence propagate errors in the projections, although the ensemble nature of our forecasting system takes account of these uncertainties to a large degree.

Despite these limitations, our results indicate that emerging safely from the SARS-CoV-2 pandemic will turn crucially on how long immunity to the virus lasts. Current variants, including the more transmissible delta variant will not affect the eventuality of pandemic fade-out if immunity is permanent or is moderately long-term in its operation. If immunity acts over shorter durations, they point, by contrast, to the possible need to consider a new post-pandemic normal that may include extending social measures and implement repeat booster vaccinations over the foreseeable future as constituting our best bets to successfully control the pandemic and return societies to close to normal functioning as possible. Such vaccination measures by reducing the time to pandemic elimination will additionally also likely reduce the opportunities for the emergence and spread of new virus variants (***Sah et al.*** (***2021***)).

Methods and Materials

Basic SEIR Model

Our previous data-driven SEIR-based COVID-19 model was extended to include the dynamics of imperfect vaccines, new genetic variants, and impacts of social mitigation measures to perform the present simulations (***Newcomb et al.*** (***2020***); ***Young et al.*** (***2021***); ***Michael and Newcomb*** (***2021***)). Briefly, the basic model simulates the course of the pandemic in a particular setting via the adaptive rate of movement of individuals through various discreet compartments, including different infection and symptomatic categories as well as immune, vaccination and death classes. Three COVID-19 variants (alpha, delta, and all others) are modeled explicitly. We also assume that each population is closed and that their population sizes remain constant over the duration of the simulations reported here. The full set of equations and description of the model are provided in a public GitHub repository (see link given below). Here, we outline how the extensions are implemented in the basic model framework.

Vaccination/Breakthrough Dynamics

The impact of vaccinations is simulated by first moving susceptible Individuals into the vaccinated compartment (V) according to the reported daily vaccination rate. These individuals are then moved from the vaccine to the booster (2nd dose booster) class at a daily rate approximating a 6-week interval between vaccine doses. The vaccines are also assumed to be imperfect, which thus allow for breakthrough infections in some individuals (***Iboi et al.*** (***2020***)). To model this, the transmission rate (β) is multiplied by a scaling factor (1 – efficacy). Average vaccination rates estimated from the last 7 days of the vaccination data in Florida were used to simulate into the future. The vaccine efficacies used in this study are given in Table 1 below (***Self et al.*** (***2021***)).

Waning of vaccine-induced immunity was explored by allowing individuals in the B state to move into a reduced efficacy state (W (see Table 3)) daily over 1 year, 2.5 years, and 5 years. The waning of natural immunity was also explored at the same waning rates. In this case, individuals are simply moved from the recovered state back to into two fully susceptible states (Figure 7). The first of these states (S) will be replenished with individuals who recover from naturally acquired infection but are yet to vaccinated. We, however, consider that these individuals will be willing to be vaccinated following their recovery. The individuals who experience breakthrough infections after being vaccinated and subsequently become infected and recover are moved into the second

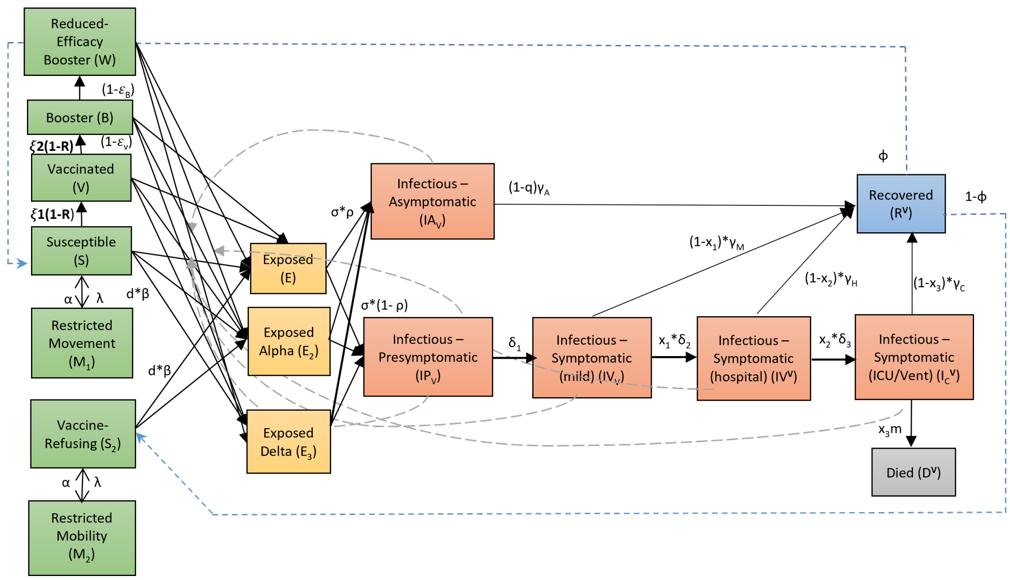

Figure 7. A simplified flowchart for the expanded SEIR model used in this study. Each compartment represents a distinct state of infection, with arrows indication flows between compartments. Full equations are given in the GitHub Repository, including how cross-immunity is modeled.

Table 3. Vaccine efficacies used in simulations

	1st Dose Efficacy	2nd Dose Efficacy	After Waning of 2nd Dose Immunity
Original Variant	75%	90%	80%
Alpha Variant (B.1.1.7)	70%	85%	75%
Delta Variant (B.1.617.2)	65%	80%	70%

susceptible class (S2). Since this class does not receive vaccinations, we also consider it to include those individuals who are unwilling to be vaccinated (9% estimated for FL (***IHME*** (***2021***).

Adding variants

Since the alpha and delta variants were dominant at various points during the pandemic, we decided to model them explicitly. This was performed using the framework described by Davies and coworkers (***Davies et al.*** (***2021***, 2020)), which essentially uses strain-specific models fitted to viral sequence data to estimate variant-specific transmission rates. We also assume that previously dominant strains provide 10% cross-protection against emerging new variants (***Davies et al.*** (***2021***, 2020). Each variant (alpha, delta, and all others) therefore has corresponding exposed (E), infectious (IA, IP, IM, IH, IC), recovered (R), and death (D) compartments along with variant-specific transmission rate estimated from sequence data, and a cross-immunity parameter by which immunity generated by individuals against previous strains confers a 10% level of protection against new emerging variants (see GitHub Repository for equations). The proportion of the population with each variant was taken from the Helix COVID-19 Surveillance Dashboard (***Helix*** (***2021***)), which compiles genetic surveillance data from each state. These proportions, along with Florida's reported case data, allowed for the model to be fit to the cases of each variant over time.

Sequential model calibration and selection

Calibration of the model to capture the transmission conditions of Florida was performed by fitting the SEIR model sequentially to daily confirmed case, death, and vaccination data assembled from the start of the epidemic until September 22nd, 2021, as provided by the Coronavirus App (***Cor***

(***2021***)). A 7-day moving average is applied to the daily confirmed case and death data to smooth out fluctuations due to COVID-19 reporting inconsistencies. A sequential Monte Carlo-based approach was used for carrying out the updating of the model by sampling 50,000 initial parameter vectors initially from prior distributions assigned to the values of each parameter for every 10-day block of data. An ensemble of 250 best-fitting parameter vectors, based on a Normalized Root Mean Square Error (NRMSE) between predicted and observed case and death data, is then selected for describing these 10-day segments of data as described previously (***Dietze et al.*** (***2018***); ***White et al.*** (***2019***); ***Newcomb et al.*** (***2020***)). Updating of the parameters is then accomplished by using the best-fitting ensemble of parameter posteriors as priors for the next 10-day block, and the fitting process is repeated. In addition, 25% of parameter vectors is drawn from the initial prior distribution to avoid parameter variance depletion during each updating episode.

Estimating social mitigation levels

The strength of social distancing measures imposed by authorities to limit contacts is captured through the estimation of a scaling factor, d, which is in turn multiplied by the transmission rate, β, to obtain the population-level transmission intensity operational at any given time in a population. This factor accounts for the effects of mask wearing, reductions in mobility and mixing, work from home, and any other deviations from the normal social behavior of a population prior to the epidemic. To set the priors for the social distancing parameter d, Google Trends search data was leveraged. Google Trends provides a normalized measure of web searches for the phrases "covid" and "covid mask" in Florida on a particular day(***Google*** (***2021***)), which we expect to correlate with levels of social distancing followed by the population. We used a range of values 10% above and below the average of the Google Trends values for the above phrases to serve as the priors for the social distancing parameter, d, before each model updating period.

Full model

The coupled differential equations governing the evolution of the full extended system, the model code used to perform the simulations, and all prior and posterior fitted parameter values for the best-fit models calibrated to data to September 22nd, 2021 are given in the Table provided at https://github.com/EdwinMichaelLab/COVID-FL-Vaccination. The ensemble of best-fitting models obtained from the sequential model calibrations was used to forecast the impacts of fully released social measures. Figure 7 provides a flowchart of the structure of the extended SEIR model described above.

Fade-out Probability Calculations

The probability of pandemic fade-out was assessed via simulation as follows. First, we used the ensemble of models that best fit the latest data (see above) to generate forward trajectories for the pandemic. For a given timestep, we then computed the fraction of those trajectories that showed strictly decreasing cases into the future. A trajectory is considered decreasing if their predicted cases are currently higher than they will be one week in the future; this weekly assessment also ensures that daily fluctuations in cases are ignored. The fraction of such trajectories is used directly to calculate the probability of elimination of the pandemic over the chosen timestep. This analysis was performed for the case of continued social distancing measures and vaccination, and also under the conditions of full release of social measures.

Estimation of Herd Immunity and the Herd Immunity Threshold (HIT)

The level of immunity required for attaining herd immunity (the HIT), and the date at which herd immunity will be achieved, were also estimated through simulation. Given that this threshold is highly dependent upon the social mitigation strategies at play – if there are strong social measures, less immunity is required to achieve consistently decreasing of cases and ultimately the fade-out of the pandemic (***Young et al.*** (***2021***)) – it is of greater interest to determine the level of this immunity or the natural HIT applicable when all social measures are stopped. To determine its value via simulation, social measures are fully released, and the date at which the median model prediction begins to show a sustained negative growth rate of cases is considered to be the date at which herd immunity is achieved. The corresponding fraction of total recovereds predicted by the model, which include both the fractions vaccinated and the fraction recovering from infection (Figure 7), on this date will then approximate the herd immunity levels in a population. Note attaining herd immunity does not imply zero transmission, but rather that after its attainment, most of the models in an ensemble will predict steadily decreasing cases.

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Competing Interests

The authors have no competing interests with regards to this work.

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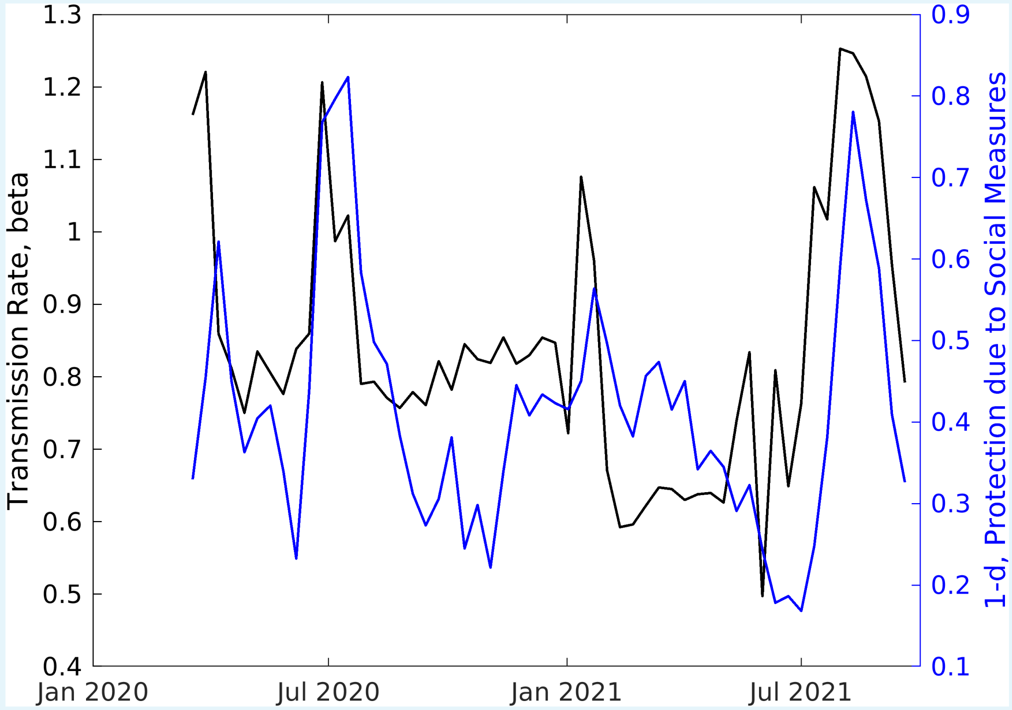
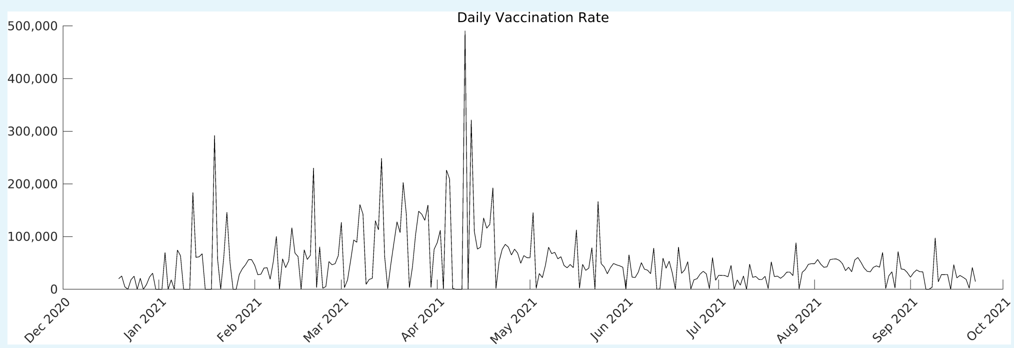
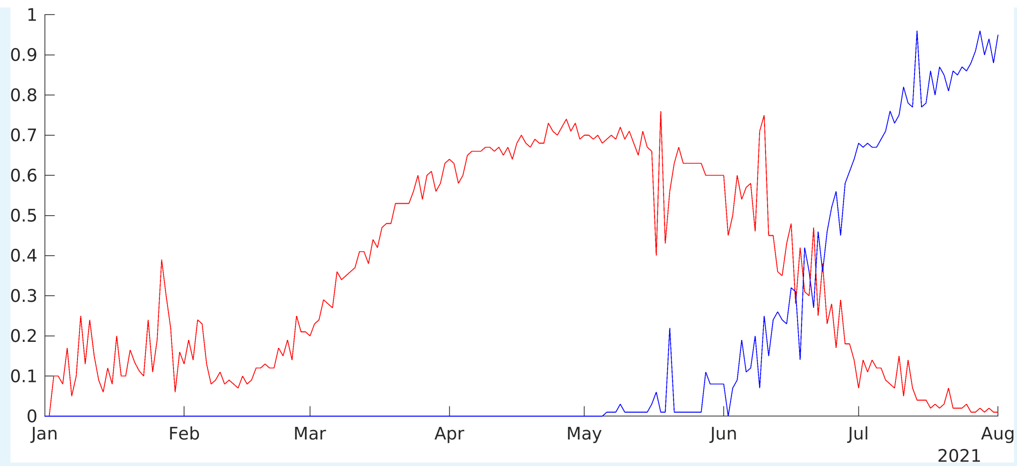
Appendix 1



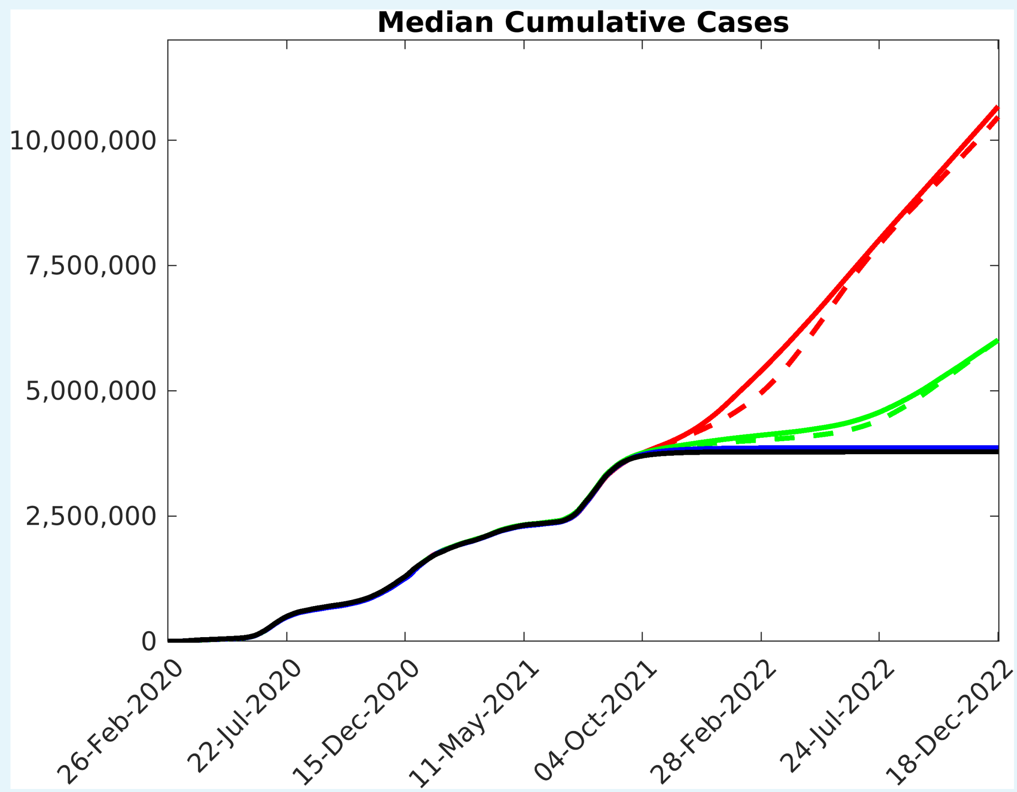
Appendix 1 Figure 1. Average estimated transmission rate (black) and protection due to social measures (1-d parameter) over time. The transmission rate is an averaged rate over alpha, delta, and all other variants. The priors on the d parameter are informed by Google Trends search data, as described in the text.



Appendix 1 Figure 2. Daily reported vaccination rate in the state of Florida, as reported by coronavirus.app.



Appendix 1 Figure 3. Proportion of alpha (red), delta (blue), and all other variants in the United States over time, as reported by the Helix COVID-19 Surveillance Dashboard.



Appendix 1 Figure 4. Cumulative Confirmed Cases in Florida. The median model prediction given current social measures and vaccination rate is given in black, while 1 yr, 2.5yr, and 5yr immunity waning periods are shown in red, green, and blue, respectively. The solid lines represent current vaccination rate, while the dashed lines represent a 1.5x increase in vaccination rate.