1   **How drivers of seasonality in respiratory infections may impact vaccine strategy: a case**
2   **study in how COVID-19 may help us solve one of influenza's biggest challenges**
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35 **Running title**: Seasonality in Respiratory Infections

Abstract

Vaccines against seasonal infections like influenza offer a recurring testbed, encompassing

challenges in design, implementation, and uptake to combat a both familiar and ever-shifting

threat. One of the pervading mysteries of influenza epidemiology is what causes the distinctive

seasonal outbreak pattern. Proposed theories each suggesting different paths forwards in being

able to tailor precision vaccines and/or deploy them most effectively. One of the greatest

challenges in contrasting and supporting these theories is, of course, that there is no means by

which to actually test them. In this communication we revisit theories and explore how the

ongoing COVID-19 pandemic might provide a unique opportunity to better understand the

global circulation of respiratory infections. We discuss how vaccine strategies may be targeted

and improved by both isolating drivers and understanding the immunological consequences of

seasonality, and how these insights about influenza vaccines may generalize to vaccines for other

seasonal respiratory infections.

1 **Text**

2 One of the pervading mysteries of infectious disease epidemiology is what causes influenza's

3 distinctive seasonal outbreak pattern [1, 2]. For a disease that annually impacts so much of the

4 globe, it is striking that we still do not fully understand the drivers of dominant dynamics. There

5 is no shortage of theories proposed and rigorously explored for what factors could yield the

6 world's various experiences of "flu season" (e.g., [3-17] among many others), but still, no one

7 theory, or set of theories, have been undeniably demonstrated to be responsible for the full

8 complexity of observed dynamics. Tailoring precision vaccination campaigns may critically

9 depend on correctly identifying these drivers.

10 In 2007, we wrote a review of the dominant theories that each, independently attempted to

11 explain influenza seasonality, highlighting the complexity of the problem, the broad categories

12 into which the proposed theories fell, and reviewing the weaknesses or gaps in the available

13 support for each [1]. One of the greatest challenges in finding support for any of the theories is,

14 of course, that there is no means by which to actually test them; evidence comes in only two

15 possible forms: correlation of prediction with observed trends and real-world contrasting

16 scenarios that allow direct exploration of controlled alternatives.

17 Consistent correlation of prediction with observed trends is the most common and accessible

18 form of evidence. While laboratory experiments can also support some critical features (e.g.,

19 duration of viable virus on surfaces outside of hosts under varying environments), whether or not

20 these features are actually the important variables in "the wild" is nearly impossible to

21 determine. Controlled experiments can determine the viability of each as a valid hypothesis but

22 cannot confirm the actual role in real-world dynamics, especially when in contrast/combination

23 with the potential varying influence of each other proposed hypothesis. Of course, the reality is

1   that no one proposed theory (or even category of theories) is likely the sole responsible factor for

2   real-world patterns, meaning that the question is not only "which of these potential factors have

3   meaningful impact on patterns of influenza in populations", but also "which combinations of

4   these factors have meaningful impact, and are there thresholds in conditions that shift the relative

5   contribution of those impacts over time and circumstance". These differences may have

6   profound implications for the success of vaccination strategies. Despite the ubiquity of influenza

7   in human populations worldwide, these are not trivial challenges to meet, and active

8   investigations continue, having truly altered the landscape of accepted theories only minimally

9   since our review from 14 years ago.

10 The second, much rarer, form of evidence comes from accidental, natural experiments that

11 perturb critical facets of the hypothesized drivers of influenza's epidemiological outcomes.

12 During 2020, COVID-19 accidentally perturbed many of the underlying features of the

13 epidemiological landscape that fosters transmissible respiratory infections and, predictably,

14 completely upended the usual patterns observed for influenza [18, 19]. The global pandemic of a

15 different infectious agent may therefore provide a rare and significant opportunity for otherwise-

16 impossible insight into the age-old question of influenza seasonality. However, this opportunity

17 is itself not without challenges. We actually have an embarrassment of riches among the facets of

18 the natural world that have been perturbed under COVID-19 and might therefore have all

19 impacted influenza. The global pandemic, and efforts to mitigate its impact, have spilled across

20 nearly every category of hypothesized driver for influenza seasonality, disrupting critical

21 elements of the basic ecology of influenza itself, altering the medical landscape within which

22 nosocomial exposure, diagnosis, and treatment are effected, and fundamentally altering the

behavioral (and thereby physical) systems of human contact (both direct and indirect) by which

influenza might be transmitted from one person to another.

While many epidemiologists braced for an anticipated "twindemic" in 2020, in which both

seasonal influenza and COVID-19 would co-circulate, wreaking havoc beyond any previously

seen [20, 21], the 2020 "flu season" was nearly non-existent [19]. Global case incidence for

influenza barely maintained the annual expected nadir in seasonal patterns for most regions, even

while cases of COVID-19 skyrocketed in many regions [22]. There are, of course, a myriad of

potential reasons for the fortunate avoidance of the twindemic devastation in 2020. One potential

theory is that interventions meant to target the spread of COVID-19, while insufficient to truly

mitigate the spread of the coronavirus, were sufficient to interrupt transmission of influenza.

Perhaps influenza simply cannot transmit effectively while a large percentage of a population are

social distancing, disinfecting surfaces, washing their hands, and covering their faces with

masks. This might itself be due to differences in viral shedding, dose/response curves needed to

enable effective transmission, or viability of extra-host virions. This set of possible interruptions

to transmission is certainly possible, however, it is also not at all the only potential explanation.

Perhaps instead so many people were simultaneously exposed to COVID-19 during what is

traditionally the season for influenza to circulate most widely that anyone who would have been

exposed to influenza had also recently been exposed to (a potentially sub-transmissible dose of)

COVID-19, and as a result had silently upregulated innate immune responses that increased

protection against infection from low-dose exposure to any respiratory infection. Perhaps many

of the people who would have been sufficiently sickened by infection from influenza to seek and

receive a diagnosis were also those who were most susceptible to COVID-19 and were therefore

removed from the population (either for medical attention or else due to death) before they could

5

be the driving spreaders of the expected seasonal influenza epidemic. Or those who would in

previous years likely have sought medical attention for flu-like symptoms instead either reported

for COVID-19 tests and, upon receiving negative results, simply never followed up with further

testing, or avoided the healthcare system entirely (whether out of fear of a COVID-19 diagnosis,

or out of fear of being exposed to COVID-19 due to seeking medical attention).

Of course, the answer is likely a messy combination of some set of these. Critically, however,

some of the existing theories for influenza seasonality make slightly different predictions for

what should happen to seasonal influenza now and how precision vaccination might respond to

curtail influenza risks from now on. Will the coming years' outbreaks be more severe because

fewer people have recently endured infection from related strains? Will shifts in internal HVAC

patterns in indoors airflow and filtering permanently alter the landscape of seasonal exposure to

influenza? COVID-19, while complicated and overwhelming to interpret, offers us a new and

exciting lens through which to study the drivers of influenza. We therefore exploit this

opportunity to return to each of the available theories about the why and how of seasonal

influenza, to dissect what the natural experiment COVID-19 provided can (and cannot), tell us

about each of them, and to guide how precision influenza vaccination strategies may respond to

this understanding going forward.

Reviewing the theories:

Broadly, the proposed mechanisms behind influenza seasonality can be divided into four

categories as relates to the COVID-19 pandemic: (1) Those which suggest influenza seasonality

should be reinforced by the measures taken against COVID-19, (2) Those which suggest it

should be disrupted, (3) Those which are COVID-19 neutral, and the most troublesome category,

(4) Those for which the answer depends on the specific scale or manner of proposed effect. We

here consider each of these cases, which theories fall into each, what each mechanism would have predicted for influenza during the 2020 absent season, and what would be predicted for the 2021 influenza season and beyond, were these to be the sole driving factors underlying the usually observed patterns.

As each of these proposed mechanisms was carefully presented and reviewed in our initial paper [1], we rely on those descriptions and do not repeat that comprehensive explanation of each theory here.

1) *Reinforcing:*

<u>Seasonal host physiology</u> - The only proposed mechanisms for seasonality in influenza that should have been reinforced during the progression and response to COVID-19 should have been those related to seasonal physiological changes in host health and capability to respond to viral challenge (e.g., due to reduction in Vitamin D levels, etc.). Since social distancing and lockdown measures in the late-Spring and Summer of 2020 vastly curtailed outdoor gatherings and activities [23], expected levels of Vitamin D in many populations should have been lower than in other years during summer and autumn months. Further, food insecurity from the economic impacts of COVID-19 likely compromised levels of other micronutrients relevant to immune function. It is therefore difficult to argue that the population entered what should have been the 2020/2021 influenza season well-equipped to fend off the virus. Indeed, seasonal host health has been proposed as one mechanism to explain the rise in COVID-19 cases in many areas in the Fall and Winter of 2020 (e.g., [24]) – if this were the only source of influenza seasonality, this mechanism would have predicted a correspondingly severe (and perhaps early) influenza season, which did not materialize.

1 Predictions Testing this Hypothesis: Reinforcement mechanisms are therefore unlikely to be the

2 operating drivers of influenza. However, if they in fact are, 2021 and beyond should bring a

3 pattern of influenza infection that is at least consistent with average, non-COVID-19 years (since

4 season-based drivers of health will continue). In this case, precision targeting of vaccination

5 should focus on correlates of seasonal host health, rather than any operative dynamic for

6 influenza itself. It may easily be the case that the same factors that make individuals more

7 susceptible infection also decrease immunological response to vaccination. Individuals should

8 then ideally be inoculated earlier in the season than exposure by itself might warrant, so long as

9 the duration of protection was sufficient to span the physiological hardships of Fall and Winter

10 seasons.

11 *2) Disruptive:*

12 Alternatively to mechanisms that would have been enhanced by the COVID-19 epidemic, those

13 that would have been disrupted by the non-pharmaceutical interventions (NPIs) put in place to

14 control COVID-19 are perhaps the easiest to defend considering the observed impact on

15 influenza seasonality – though matching the dynamics one would expect under the circumstances

16 is far from definitive proof.

17 Global travel patterns - The seasonal dissemination of influenza via the air travel network is

18 perhaps the most obvious mechanism to be disrupted by the COVID-19 epidemic. A broad series

19 of travel bans were put into effect early in the epidemic, and traveler throughput through TSA

20 checkpoints, one measure of air traffic patterns, dropped precipitously [25] (Figure 1). This

21 disruption would have prevented both the international and domestic propagation of influenza

22 virus through air travel.

1   One complication to this is the increase in COVID-19 cases corresponding to holiday travel in

2   November and December of 2020 where travel, while reduced, was still relatively commonplace

3   and was not seen to lead to a concomitant rise in influenza. This perhaps limits the scope of

4   support for this mechanism to longer temporal scales of impact.

5   Predictions Testing this Hypothesis: Should global travel be the main driving mechanism

6   yielding seasonality in influenza, 2021 and future seasons are not easy to predict. Fluctuations in

7   travel within national borders are likely to continue through the coming years due to increased

8   costs, altered availability in travel routes, and decreased demand (whether due to alterations in

9   business practices or individual personal hesitancy) [26, 27]. International travel is subject to

10   each of these impacts and is further likely to shift over time as nations implement different travel

11   policies, some likely based on COVID-19 vaccination status of the traveler, others potentially

12   based on COVID-19 prevalence in the originating nation, and others based on social and political

13   ideology [28]. How these strikingly different rates of expected travel and different patterns in

14   geographic connection due to travelers may play out in affecting influenza cannot lead to

15   rigorous predictions. Widespread acceptance of travel as a driver of international disease

16   transmission, however, may increase willingness to vaccinate against preventable infections.

17   While unlikely to become a requirement for travel, campaigns encouraging travelers to be

18   vaccinated against influenza prior to travel may lead to increased uptake in voluntary

19   vaccination.

20   *3) Neutral:*

21   Multiple mechanisms among those proposed as drivers of influenza seasonality are likely to be

22   neutral in the context of COVID-19.

Influenza evolution/immune memory loss: Mechanistically, the evolution of the influenza virus and the accompanying host immune response should, in isolation, have been independent of the measures taken to control COVID-19. The prevalent, circulating influenza viruses in the 2019-2020 influenza season had ample mutation and immune-escape opportunities during that season, and by the time NPIs were in widespread use, the northern hemisphere influenza season was well past its peak. This should have set the stage for the coming 2020-2021 influenza pattern. An antagonistic immunological response to influenza co-infection with COVID-19 infected individuals, or else the prevention of infection due to upregulated innate immune responses following COVID-19 exposure, might explain the muting of this mechanism (though some studies suggest that broad anti-viral immune responses in COVID-19 patients are fairly rare [29]). Other viral interference mechanisms might also be explanatory, but once again there are studies suggesting that, at least early in the initial COVID-19 outbreak, co-infection was relatively common [30].

Global weather patterns: Increased influenza transmission by the El Niño Southern Oscillation (ENSO) should have been uncorrelated with the COVID-19 pandemic, as the most recent ENSO occurred in 2018-2019, well prior to the epidemic. ENSO's semi-periodic nature suggests that any impact it has on influenza seasonality will similarly be uncorrelated with the scaling back of anti-COVID-19 NPIs. Like the dramatic climatic fluctuations brought about by ENSO, more regular seasonal and climatic factors such as oscillations in temperature and relative humidity – with the attendant impacts on viral survival – should be relatively unchanged during the COVID-19 period which, while having noted impacts on pollution levels and associated environmental health risks [31], is unlikely to have dramatically changed seasons themselves. If these factors

1   are the *primary* drivers of the seasonal periodicity of influenza, it seems reasonable to assert that

2   these should remain unchanged.

3   <u>Predictions Testing these Hypotheses</u>: Since each of these mechanisms should be unaffected by

4   COVID-19, predictions for both the past and the coming influenza seasons should be consistent

5   with pre-COVID-19 patterns, in the absence of other interruptions. However, the impact of these

6   two factors on targeted vaccination protocols would diverge, with strain surveillance itself being

7   critical to the timing and coverage recommended in the case that temporal patterns are driven by

8   evolution and immune memory loss, while global weather patterns are truly, definitionally

9   seasonal and responsive precision vaccines could be determined on an annual cycle based solely

10   on annual climatic conditions.

11   *4) Conditional:*

12   Lastly, among the proposed mechanisms that might yield observed seasonal patterns in influenza

13   incidence, those that depend on the scale and manner of the effect include:

14   <u>Atmospheric transport</u>: The hypothesis that influenza is propagated via the bulk upper-

15   atmospheric transport of aerosols is particularly hard to evaluate in the context of the COVID-19

16   pandemic. While the air currents themselves should have remained largely unaffected by

17   COVID-19, the theory depends on the existence of large volumes of aerosolized influenza –

18   which leads to the somewhat circular argument that the hypothesis predicts that there wouldn't

19   be an influenza season because there wasn't an early increase in influenza incidence anywhere

20   on the globe that could then cascade into other continental outbreaks via atmospheric transport.

21   <u>Seasonal crowding behavior</u>: In contrast, the belief that crowding and increased close contact

22   drives influenza seasonality – usually based on the belief that humans gather in denser, indoor

1   groups during colder months (though, strangely, not that humans gather indoors in air-

2   conditioned rooms during the peak of heat in the summer months; [32]) – should have been

3   either positively or negatively impacted by COVID-19 related NPIs depending on what *scale* of

4   crowding we consider. If the crowding that drives influenza seasonality is based on larger groups

5   of individuals, the widespread prohibitions of mass gatherings, work from home policies and

6   school closures should have vastly reduced the population's exposure to large crowds [33].

7   Correspondingly, if instead it is primarily household-level crowding that drives influenza

8   seasonality, these very same policies likely increased the density of household contacts,

9   especially during the winter when fewer outdoor activities are generally available [33].

10   Seasonal environmental conditions: The same question of scale exists for the potential role of

11   indoor heating. Intensified household exposure to residential furnaces with relatively weak

12   filtration systems due to working from home policies and the closing of indoor group spaces

13   during the colder Fall and Winter months would, if household-based transmission were the

14   primary driver of influenza seasonality, increase the likelihood that a single household

15   introduction would become a micro-epidemic, have exacerbated this phenomenon. If the primary

16   driver is instead the mass infection of individuals in a single setting that then propagates outward

17   (as with the Amoy Gardens superspreading event during the SARS epidemic; [34]) to seed the

18   epidemic across communities, the relative dearth of crowded indoor spaces may have

19   significantly dampened the 2020-2021 influenza season.

20   Predictions Testing these Hypotheses: Unsurprisingly, the conditional nature of the action of

21   each of these hypothesized mechanisms also implies that predicted impacts on the coming

22   influenza seasons will depend on the scale and manner of effect. Similarly, precision vaccination

23   campaigns would target the independent drivers, if validated.

Of course, the great caveat to consideration of many of these mechanisms for the 2020 influenza season is that prevention of transmission may interrupt spread, but may not be the driving factor that would still have interrupted seasonal patterns, even had spread been able to continue. The lens of COVID-19 as a means by which to explore influenza cannot allow us to explore disambiguated interruptions, but that certainly does not leave us without benefit from consideration of the individual cases. The most important effort may, in fact, lie in whether these predictions allow for disambiguation among the hypothesized factors under the alterations COVID-19 has initiated. Given these known changes, we can consider whether we could either meaningfully strengthen or else refute support for any of the proposed mechanisms should the predictions they suggest fail to materialize. As we watch the trends materialize over the 2021 influenza season, it is likely that at least a few of these potential predictions will be falsified. For those with clear directional predictions, this will help eliminate from consideration the guiding hypothesized mechanism. For those that depend conditionally on scale, even narrowing the potential scale and manner of effect will be a significant improvement in scientific understanding, allowing the next round of hypothesis testing to eliminate entire levels of analysis and intervention from consideration.

Using COVID-19 to more broadly advance our understanding of influenza

SARS-CoV-2 represents the first large scale pandemic driven by a novel virus of likely zoonotic origin in the current molecular biologic era and thus provides insight into previous historic events involving other viruses, to the extent that there is similarity between the pathogens. For the initial influenza encounter these similarities would include the RNA virus nature of both pathogens as well as the physical aspects of respiratory virus spread from host to host.

An interesting question arises from considering the possibility of eradication or disappearance. It has been suggested recently that mask wearing in response to Sars-Cov2, may have led to the disappearance of two influenza strains [35]. This possibility raises the parallel question about sterilizing immunity, which is often the normal assumption made when thinking about influenza control. If, instead, immunity from prior influenza infection was likely to reduce the likelihood of developing detectable signs and symptoms but *not* fully prevent reinfection, then undetected circulation of influenza would be expected to drastically alter predicted patterns of seasonality.

The current SARS-CoV-2 pandemic can be instructive for influenza modelers and historians (just as these considerations may similarly aid our ability to understand and predict the eventual dynamics of COVID-19, see Appendix A). A similar scenario most likely played out for the ~1500 putative influenza pandemic although the various waves spanned decades instead of years. New naïve populations with possibly distinct polymorphisms (including HLA) and different exposure histories were encountered more slowly and may have required some modifications by the virus to achieve high transmission rates. The 1918 influenza pandemic also showed such wave-like advances [36]. Left in the wake of these expansions were the virus strains and substrains that continued to evolve over time. The Sars-Cov2 pandemic has forced us to rethink global preparedness plans with respect to testing capacities, testing quality, speed, cost [37], demonstrating how maintaining testing capabilities will be essential to the control of seasonal influenza and other respiratory pathogens. A two-pronged testing strategy—diagnostics and screening—should become the playbook for responding to outbreaks and for modeling and forecasting flu.

An interesting possible future direction involves potential interactions between SARS-CoV-2 and influenza. This can range from simple non-interactive co-existence, constructive interactions

where infection with one facilitates infection with the other, or possible interference. In late winter – early spring of 2020 there was robust infection with influenza and Sars-Cov2 infections did not rise until the influenza was on the wane. While one (unmasked) influenza season is far from definitive, the influenza season of 2020-21 reappeared at expected time yet with the substantially lower intensity.

Between September, 2020 and April 22, 2021, only about 2,000 cases of influenza had been recorded, according to CDC data, even though in recent years, the average number of cases over the same period was about 206,000 (see Figure 2). The low influenza season reduce the typical boost for memory retention in the general population and made it difficult for scientists to decide the optimal combination of influenza strains for upcoming influenza vaccines. Thus, the lack of exposure could make the population more susceptible to virus when it returns, or to shift the seasonal curve due to rapid changes in contact rates when non-therapeutical interventions (NTI) are lifted. It likely that with the changes in seasonal population migration due social calendar, the seasonal pattern of influenza could substantially vary geographically [38, 39].

The pandemic revealed several important aspects of data collection and reporting and reliance on data for modeling purposes. Reporting of influenza dropped quite drastically in US and worldwide. While primarily driven by NTIs, in part the drop could be also attributed to resource reallocation. The global reporting of various influenza strains vary due to both: presence of a strain of interest and national capacity to detect and report – a challenge noted for the influenza pandemic of 2009 [40].

Because of the focus of the CD8 memory repertoire on a relatively immutable epitope, seasonal exposures to influenza affect the generation, maintenance, and finally senescence of the

1   repertoire [41-43]. In childhood, each exposure to infection helps the immune system improve

2   protective response, whereas later in life, immune coverage is likely already well-developed and

3   protective, and does not improve in overall function with each next exposure. This well-

4   developed protection, however, does exhibit senescence associated with later years [44]. With

5   the passage of time, the influenza memory repertoire degrades, and re-exposures may once again

6   lead to substantial morbidity and possibly mortality. A footprint of past major outbreaks of

7   influenza was noted in our early work, when those who were children during influenza pandemic

8   of 1918 or in 60s exhibited different patterns of pneumonia and influenza (P&I) mortality as

9   older adults [45]. During the COVID-19 pandemic, the seasonal exposure to influenza was

10   disrupted and is likely to leave a specific footprint on each subpopulation.

11   Mask-wearing mandates, school closures, limited social outings and other NTI strategies had

12   resulted in substantially reduced respiratory pathogen transmission in all age groups. Viruses

13   including influenza A, influenza B, parainfluenza, norovirus, respiratory syncytial virus (RSV),

14   human metapneumovirus—all appear to be circulating at or near levels lower than ever

15   previously measured. The same is true for the respiratory bacteria that cause pertussis, better

16   known as whooping cough, and pneumonia. In 2019, during the third week of December, before

17   the coronavirus struck the United States, the CDC's network of clinical labs reported that 16.2

18   percent of the 29,578 samples tested were positive for influenza A. During the same week in

19   2020, the rate was 0.3 percent. Before the pandemic, in regular influenza seasons we had noted

20   that in the school term weeks average weekly testing were significantly higher as compared to

21   holidays [6]. The dampening of tests during the winter break was evident in all ages and

22   especially in children and young adults. Overall, the effect of social calendar depends on the

23   alignment of seasonal influenza peak to individual holiday timing. These results indicate that

better understanding of the confluence of social factors (e.g., in-school mixing, travel, and inter-household, multigenerational gatherings) governing influenza transmission in specific age groups should improve influenza prevention measures. The pandemic has demonstrated the degree of acceptance of various NTIs and offered lessons for the future.

Rapid implementation of mass vaccination for COVID-19 and lessons from influenza vaccination are revealing valuable insights. In brief, people who did not get an influenza shot are more likely to intend to not get their COVID-19 vaccine, and people who have their COVID-19 vaccine are more likely to have gotten their influenza shot [46]. Our large-scale studies demonstrate the importance of childhood vaccination to reduce exposure and influenza-related hospitalizations in older adults [47, 48]. Yet, the vaccination coverage could be substantially expanded in all age ranges [49].

During the century since the end of the Great Influenza outbreak, the average human lifespan has doubled. The pandemic is projected to reduce life expectancy by 1 year in US population [50] and has changed the demographic structure of the population at risk for both influenza and relevant comorbidities. Prior the pandemic the common knowledge was that as the overall population getting older due to increased life expectancy, the number of all cause hospitalizations peaked for patients of 80–82 years of age. It is likely that immune system impairments may accumulate with time and multiple pathology is mounting with age. We observed that older adults with severe comorbidities, including cancer, HIV, cognitive impairments had higher mortality due to P&I potentially due physiological changes, inability to communicate the discomfort, inability to recognize atypical symptomatology, lack of proper care [51, 52]. It has been already noted that different subpopulations even among older populations were affected disproportionally [47, 50, 53]. There is a strong link between demographic

structure and hospitalization patterns for P&I in the older adults with respect to their residential location[38, 51, 53]. While the number of death due to COVID-19 were disproportionally high for older adults, the pandemic could influence accelerated aging for those who survived COVID-19. Influenza modeling, and precision vaccination planning, should take into account drastic changes in population composition post-COVID-19 [54]. This is especially true when selecting among the potential desired outcomes of vaccination campaigns. For example, preventing the greatest number of infections may dictate a drastically different strategy from preventing the greatest numbers of severe outcomes from infection (including deaths).

Conclusion

Precision vaccination relies on understanding the drivers of etiological, epidemiological, immunological, and virological dynamics of infection. Considering the ongoing mystery of emergent seasonality in influenza forces us to consider each of these drivers in a new light. COVID-19 has provided a unique context in which to test the broad set of existing hypotheses for why and how influenza seasonality exists, and to increase our understanding about how vaccination could be tailored to exploit those same drivers to increase efficacy in desired individual patient and broad public health outcomes. It will take many years of observation and analysis to understand the what, why, and how of the potential impacts COVID-19 might have on seasonal patterns in influenza, but this natural experiment may be one of our best opportunities to re-examine our understanding of temporal patterns for this fascinating disease.

Conflict of Interest Statement

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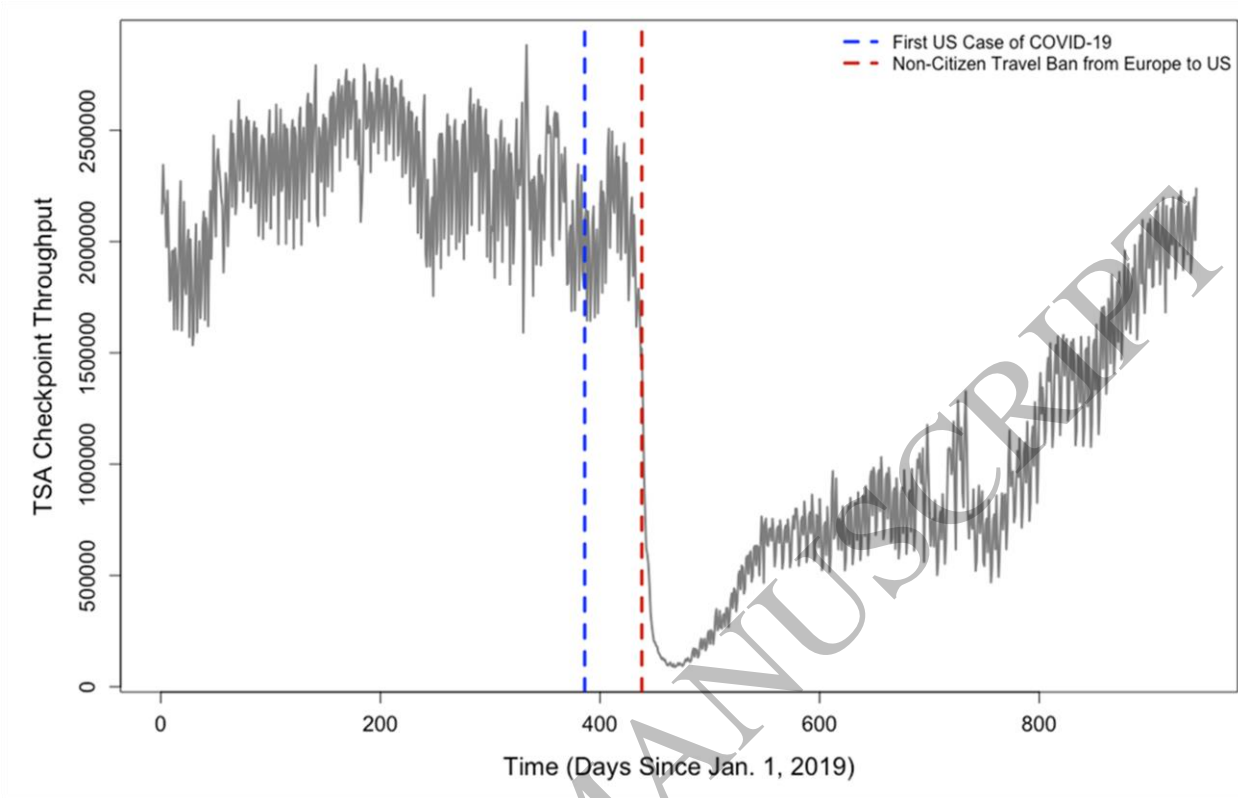
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2 **Figure Legends**

3 **Figure 1**. Travel volume in the United States as represented by throughput through security

4 screening stations (as reported by the US TSA). Travel volume shows a marked drop-off as the

5 virus begins to spread in the United States and a ban on non-citizens traveling from Europe to the

6 US, slowly recovering though not yet reaching pre-pandemic levels.

7 **Figure 2**. Weekly reporting of influenza incidence (black line) from 13 August 2018

8 (Epidemiological Week 33 of 2018) through 20 June 2021 (Week 24 of 2021) and COVID-19

9 (red line) from 20 January 2020 (Week 4 of 2020) through 20 June 2021 in the United States:

10 upper panel – laboratory confirmed cases for all detected strains; middle panel – Type A

11 influenza; low panel – Type B influenza; all values are shown using a log10 scale. Data source:

12 World Health Organization's (WHO) Global Influenza Surveillance and Response System's

13 (GISRS) FluNet influenza virological surveillance database (courtesy of Ryan Simpson, MS,

14 Friedman School of Nutrition Science and Policy).

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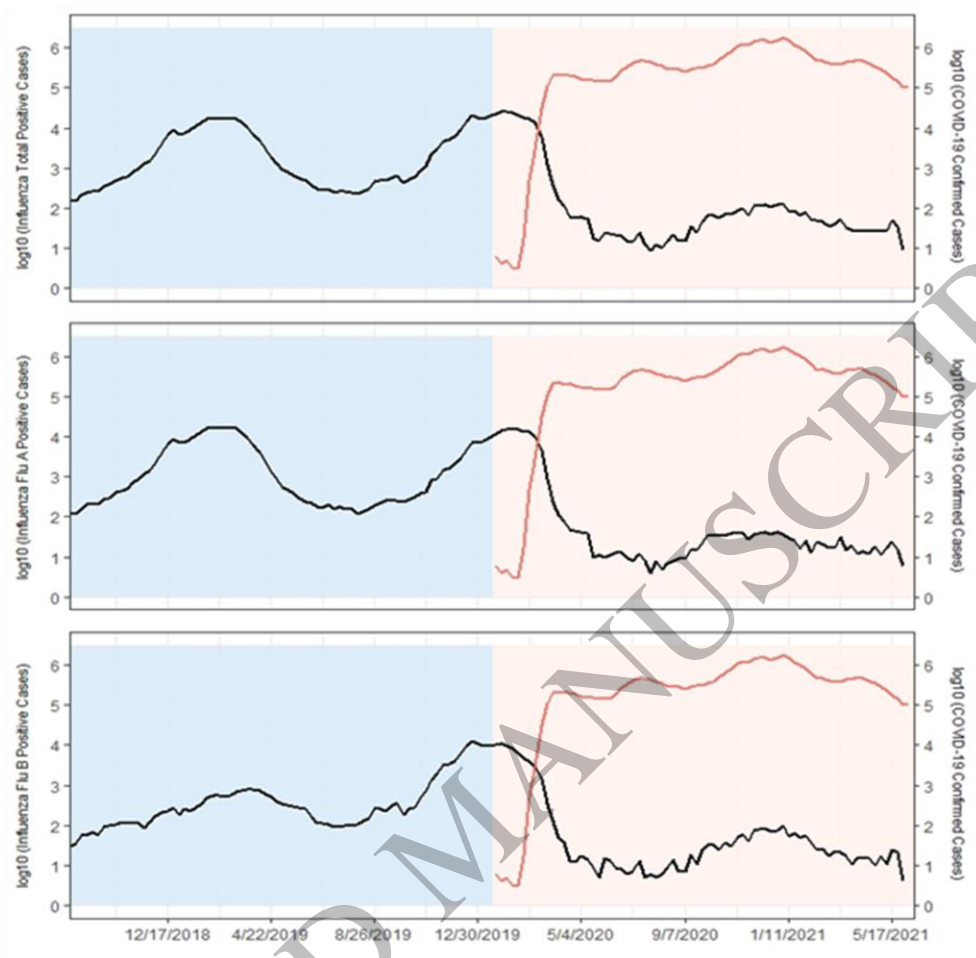2   **Figure 1**
3   **165x106 mm (.96 x DPI)**

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2 **Figure 2**
3 **130x126 mm (.96 x DPI)**