Increasing herd immunity with influenza revaccination

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SUMMARY
Seasonal influenza is a significant public health concern globally. While influenza vaccines are the single most effective intervention to reduce influenza morbidity and mortality, there is considerable debate surrounding the merits and consequences of repeated seasonal vaccination. Here, we describe a two-season influenza epidemic contact network model and use it to demonstrate that increasing the level of continuity in vaccination across seasons reduces the burden on public health. We show that revaccination reduces the influenza attack rate not only because it reduces the overall number of susceptible individuals, but also because it better protects highly connected individuals, who would otherwise make a disproportionately large contribution to influenza transmission. We also demonstrate that our results hold on an empirical contact network, in the presence of assortativity in vaccination status, and are robust for a range of vaccine coverage and efficacy levels. Our work contributes a population-level perspective to debates about the merits of repeated influenza vaccination and advocates for public health policy to incorporate individual vaccine histories.

Key words: Disease control, epidemiology, influenza (seasonal), mathematical modelling, vaccines.

INTRODUCTION
Influenza is a serious public health threat throughout the world. In the United States alone, seasonal influenza contributes to about 30 000 excess deaths per year on average [1], and accounts for millions of lost work days each year [2]. Controlling influenza is a multifaceted effort but seasonal influenza vaccination has been the centerpiece of influenza control efforts in the United States for the past 60 years. Vaccine coverage of only 40% is believed to reduce the risk of influenza illness by about 60% in the whole population [3].

While the impact of overall influenza vaccine coverage levels in a single season has been studied in detail [4, 5], the consequences of repeated seasonal influenza vaccination of the same individuals have not been studied as extensively. Most research on repeated vaccination has considered this problem from an immunological or purely statistical perspective and not considered potential population-level consequences of repeated vaccination. Serological studies in children and experimental challenge studies in animal models suggest that vaccination may weaken the immune response to infection and hamper the development of heterosubtypic immunity in particular [6–9]. Numerous studies have suggested that prior vaccination reduces the effectiveness of current season vaccination [10–13], but Keitel et al. [14] and Voordouw et al. [15] found that repeated vaccination
contributes to increased protection. Epidemiological estimates of vaccine effectiveness, especially when stratified by prior vaccination status or infecting strain, are generally quite imprecise, making it difficult to draw robust conclusions. Discrepancies may be explained by the antigenic distance hypothesis, which depends on positive and negative interference between vaccine strains [16].

A thorough understanding of the merits of vaccination strategies may require considering their consequences across multiple seasons. Carrat et al. [17] assumed no long-term immunological benefits from repeated seasonal influenza vaccination, and modelled long-term effects of vaccination strategies which prescribe vaccinating adults and children, such as the strategy recently adopted in the United States. Their analysis suggests that vaccinating people throughout their lives prevents them from developing natural immunity to influenza and therefore increases the risk of infection at older ages. Counterintuitively, their results suggest that given the greater risk of mortality associated with influenza at increasing ages, vaccination at all ages may actually increase influenza mortality. However, their analysis does not directly model influenza epidemics and does not account for any herd immunity impacts of higher vaccination rates or rates of individual-level revaccination.

Epidemiological models have been used extensively to study vaccination and other influenza control strategies and consider targeted vaccination to minimize morbidity, mortality, or economic costs [18–21]. Some mathematical models as well as epidemiological data suggest that targeting influenza vaccination towards school-age children may be a preferred strategy, as children are the age group most likely to be infected with influenza and to transmit it to others [18, 20]. Others have advocated for a strategy that minimizes mortality by targeting those most at risk for complications and death [19, 21]. However, most models of influenza vaccination have focused on single epidemics and hence not accounted for the rate of revaccination (but see Fung et al. [22]). While the present study was under review, Yamin et al. published results from a similar modeling analysis, focusing on vaccinating individuals infected in the previous season, and not explicitly manipulating revaccination [23]. Moreover, modelling revaccination inherently requires a modelling framework such as contact network modelling that explicitly models individual hosts. Recent theoretical research using contact network models has shown the significance of modelling epidemics in series, when natural immunity from past epidemics influences future ones [24, 25].

In this study, we consider whether the rate of revaccination, which we define as the proportion of first-season vaccine recipients who are vaccinated in a successive influenza season, may be epidemiologically relevant. We present a two-season mathematical model to explore the consequences of influenza revaccination on herd immunity and the mechanisms driving them. Our theoretical study suggests that revaccination indeed reduces the public health burden, and that this result is robust with respect to variation in contact structure, vaccine efficacy, vaccine coverage, vaccine assortativity, and levels of natural immunity. Our work thus contributes a population-level perspective to debates about the merits of repeated influenza vaccination and advocates for public health policy to incorporate individual vaccine histories.

RESULTS

To assess the epidemiological relevance of revaccination rates, we present a contact network model for two consecutive influenza seasons. In the contact network model, each individual is represented as a node, and influenza-spreading contacts or interactions are represented as edges (Fig. 1). Prior to the first influenza season, all individuals in the population are susceptible to infection. A proportion of this population is protected by pre-season vaccination. We assume that vaccine-induced immunity is fully protective in a season and is protective only in the season in which vaccination occurs, but that natural immunity confers protection in the season following infection (further details are provided in the Methods section, and sensitivity of our results to these assumptions is presented below). Outbreaks are simulated until a large epidemic (i.e. $\geq 5\%$ of individuals infected) occurs. Following a first-season epidemic, vaccination is implemented again prior to the second-season outbreak. The identity of the second-season vaccine recipients is chosen based on the revaccination rate ($r$, ranging from 0% to 100%), and is implemented randomly. We assume that the level of vaccination coverage is constant across both seasons, supported by the National Health Interview Survey which shows that influenza vaccination coverage in the United States has been quite consistent from the 2007/2008 season to the 2011/2012 season [26]. We record results from second seasons in which a large epidemic occurred. We focus on the size of second-season
epidemics because the rate of revaccination inherently cannot have any bearing on first-season outbreaks.

When the model is applied to a synthetic (computationally generated) exponential random contact network (details in Methods section below), we find that second-season epidemic sizes decrease as the rate of revaccination increases (Fig. 2). This result indicates that the rate of revaccination is indeed epidemiologically relevant, and we explore below some of the mechanisms leading to this effect.

Explaining the effect of revaccination: ‘wasting’ vaccine

One possible cause of the decrease in second-season epidemic sizes with increasing revaccination could be more efficient use of vaccine: individuals with natural immunity from first-season infection are less likely to also be vaccinated for the second season, thus preventing ‘wasting’ vaccine. When revaccination is complete ($r = 100\%$), no individual can be both naturally immune (i.e. protected due to first-season infection) and have second-season vaccination (given our assumption of a fully protective vaccine). As a result, more revaccination leads to fewer susceptible individuals prior to the second season, which indicates a more efficient use of vaccine (Fig. 3a).

Here, we test if revaccination has an impact on epidemic sizes even when the number of susceptible individuals is constant. We do this by comparing two models of vaccination that differ in the way doses of vaccine are distributed after revaccination. Universal vaccination distributes these remaining doses randomly, while preferential vaccination distributes the doses to previously uninfected individuals. We show results from preferential vaccination only in Figure 3b and elsewhere in this study we use only the universal vaccination approach.

We find that as the rate of revaccination increases, the proportion of susceptible individuals infected during the second season decreases regardless of whether individuals with natural immunity are vaccinated (Fig. 3). While the effect of revaccination is most pronounced in the universal vaccination scenario, a decrease in epidemic size is also evident under the
preferential vaccination scenario. This result suggests that the increasing number of protected individuals does not fully explain the relationship between revaccination rate and epidemic size, and that higher revaccination rates also confer greater indirect protection to susceptible individuals.

Efficiency of vaccination schemes: connectivity of susceptible individuals

It is well-understood that public health measures such as vaccination can demonstrate an impact beyond those directly protected, to indirectly protect a larger community. The extent of this indirect protection, or herd effect, can be quantified in our model by comparing second-season epidemic sizes at elevated rates of revaccination to second-season epidemic sizes when the level of revaccination is equal to the overall coverage level, which is the level of revaccination expected if vaccination is not affected by previous vaccination status. Figure 4 shows that as revaccination increases, the population-level efficacy of indirect protection increases as well.

To better understand why higher rates of revaccination indirectly protect susceptible individuals, we explore the degree (number of contacts or edges) of susceptible and protected (vaccinated or naturally immunized) individuals in the network. Higher degree nodes are more likely to be infected during the first season and thus be naturally immune in the second season (Fig. 5a) [25, 27]. As a result, remaining susceptible nodes have lower degree, on average, than both naturally immune individuals and individuals vaccinated during the first season (Fig. 5a). In a population connected as an exponential random network, with complete revaccination, susceptible individuals in the second season have an average degree that is 15% smaller than that of susceptible individuals in the first season. However, when individuals are not revaccinated, they increase the average degree of susceptible individuals (Fig. 5b). This, in turn, decreases the strength of the herd effect in the network, because when high degree nodes are not protected, the epidemic is able to spread further [28].

Robustness in realistic populations

To explore the robustness of our findings, we test our hypotheses on an empirical contact network model as well as with realistic values of epidemiological parameters. The empirical network represents an urban population based on data for the city of Vancouver, British Columbia, and is built from age-specific, activity-based interaction patterns relevant to the spread of an influenza-like illness [25, 29]. Bansal et al. [25] find that while the Vancouver-based model has a higher density of contacts, age-specific contact patterns are captured well in the model compared to empirical data from studies on contact structure.

Based on this contact network, we assume age-specific vaccine efficacy and coverage rates based on the 2006 and 2011 influenza seasons in the United States, as well as levels of natural immunity based on empirical estimates from recent studies (details in Methods section). Our findings in this scenario, based on the Vancouver host population and empirical parameters, are qualitatively similar to those found previously: increased revaccination decreases the proportion of individuals infected (Fig. 6). While we are not aware of any studies that focus on estimating influenza revaccination rates in large populations, we have been able to infer approximate revaccination rates from a variety of studies. Adjusting revaccination rates for varying coverage levels, we estimate plausible excess revaccination rates ($r'$) of 39–78% (details provided in Methods section). (We highlight these estimates for context in Figure 6.) While the impact of revaccination is more muted due to the use of an imperfect vaccine with moderate levels of coverage, these results illustrate
that revaccination does indeed reduce the burden on public health (for realistic estimates of \( r^* \)), and has the capacity for a larger impact.

In addition, we conduct sensitivity analyses to assess whether our findings are robust with respect to partial natural immunity (Supplementary Fig. S1), vaccine efficacy (Supplementary Fig. S2) and vaccine coverage rates (Supplementary Figs S3 and S4). We also studied whether assortative vaccination, a phenomenon that has been observed empirically [30], affects the relationship between revaccination and epidemic size (Supplementary Fig. S5). In terms of network variables, we consider the impact of variation in network size (Supplementary Fig. S6) and variance in node degree (Supplementary Fig. S7). Finally, we assess the consequences of rewiring the network between seasons (Supplementary Fig. S8).

In general, we find that the decrease in epidemic size due to revaccination is strongest when both vaccine efficacy and natural immunity are complete and when networks have degree distributions with high variance. In addition, lower vaccine coverage appears to increase the effect of revaccination on the total number of cases, highlighting that higher revaccination rates can be used to compensate for low coverage rates (e.g. the epidemic size for a vaccine coverage rate of 50% with no revaccination is equivalent to the epidemic size for a vaccine coverage rate of 30% with full revaccination) (Supplementary Fig. S4). Finally, we observed that the relationship between revaccination rate and epidemic size is robust to assortative vaccination, network size, and rewiring, which corresponds to the fact that an individual’s contacts may change from season to season.

**DISCUSSION**

Using a mathematical modelling framework that accounts for the consequences of past epidemics on future disease outbreaks (Fig. 1), we have considered the epidemiological impact of influenza revaccination. Our work suggests that implementing greater rates of revaccination may contribute to reduced outbreak sizes (Fig. 2), both by reducing the overall number of individuals who are susceptible by using vaccine more efficiently (Fig. 3), and by increasing the extent to which more connected individuals are protected (Figs 4 and 5). We also show that similar results are obtained in populations with more realistic contact relationships.
structure, and using empirical estimates of natural immunity levels, less than ideal vaccine coverage levels, and vaccine efficacy levels from recent influenza outbreaks (Fig. 6). While we have focused our attention on the impact of revaccination on the total incidence of influenza, we expect similarly positive results for other metrics of public health impact (e.g. peak incidence and outbreak duration). See Yamin et al. for an additional perspective on the implications of natural immunity levels on vaccination strategies [23].

The process described in this study can be thought of as a partial fragmentation of the contact network by first-season vaccination and, especially, the random vaccination of highly connected individuals. Infection then spreads, working its way through the most connected parts of the network, but its path is constrained by first-season vaccination. When previously vaccinated individuals are not revaccinated (i.e. when \( r \) is low), previously protected fragments of the network are made vulnerable. This compromises the strength of herd protection, thereby creating new paths through the population along which infection can spread during the second season, leading to larger second-season epidemic sizes. The robustness of our findings to rewiring between seasons confirms that the process described here is driven by the average degree of vaccinated vs. susceptible nodes, not by the particular topology in the network (Supplementary Fig. S8).

More generally, we have demonstrated that mathematical models to develop and test influenza vaccination schemes should take into account previous vaccination status, as the distribution of vaccination in a population, even if it is random, can shape patterns of natural immunity. In turn, patterns of natural immunity are not random and drive the frailty of the host population [25, 27]. Frailty is defined as the extent to which highly connected individuals are at risk of infection [27]. These findings also reinforce previous work that highlights the need for shifting influenza control strategy with the epidemiological structure of a population and for targeting those most likely to be infected [25]. While this study focuses on human influenza in particular, the population-level consequences of revaccination rates may be relevant to other infectious disease systems with complex multi-strain natural and vaccine-induced immunity dynamics, such as dengue and even swine influenza or foot-and-mouth disease in livestock. This study is relevant to public and animal health policy because it contributes a population-level perspective to debates about the merits of repeated influenza vaccination.

One of the limitations of this study is that in real populations, there is no corresponding first season of seasonal influenza in which natural immunity does not exist. However, our findings are relevant to seasonal influenza vaccination policy immediately following an influenza pandemic during which widespread vaccination occurred. In general, this is an area of study ripe for further empirical and theoretical work: a better understanding of the longitudinal distribution and properties of natural and vaccine-induced immunity to influenza in empirical contact networks would significantly enhance modelling efforts. In particular, a better understanding of the mode by which natural and vaccine-induced partial immunity act (i.e. polarized or leaky) would aid these efforts. However, previous work demonstrates that our results may only be quantitatively but not qualitatively affected by knowledge of this mode [24]. Moreover, this model assumes that the host population is closed and that the network structure is constant across both seasons. We relax the latter assumption in our rewiring sensitivity analysis (Supplementary Fig. S8). Presumably those assumptions become less tenable as models take into account more seasons in series. However, the mechanism of

![Fig. 4. Strength of the herd effect (or, indirect protection) at different levels of revaccination. Efficacy is calculated as \( 1 - RR \), where \( RR \) is the relative risk, calculated as the ratio of incidence in unvaccinated individuals at the specified rate of revaccination and incidence in unvaccinated individuals when the revaccination rate is equal to the vaccine coverage (i.e. \( r = 0 \)). This Figure is based on results from 2000 simulated second-season large epidemics on a single 5000 node exponential random network with \( T_1 = 0.09, T_2 = 0.18, E = 1.0, Q = 1.0, \) and \( C = 0.25 \).]()}
indirect protection we have identified relates to the average connectivity of immune and susceptible individuals, not necessarily their particular place in the network. Very little is known about how contact networks change over time; but limited evidence suggests that the number of close friends or contacts is fairly stable over the time scales relevant to this study [31] (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4503306/). Finally, this model does not explicitly take into account viral evolution (viral evolution is an implicit factor only to the extent that vaccine failure is due to antigenic drift, and the degree to which natural immunity is retained). Presumably, the validity of the assumption that vaccine-induced immunity is season-specific and that natural immunity is effective across seasons varies depending on the particular pair of seasons under consideration (and is tested partially in our sensitivity analysis).

While vaccinating individuals with large numbers of contacts is arguably advantageous regardless of the individual’s immunological history, this study indicates that it may be especially important to vaccinate individuals who, by virtue of their occupation or living arrangements, are likely to have a high number of contacts and who have been vaccinated previously. Due to past vaccination, such individuals may be less likely to have natural immunity and, if not vaccinated, could infect large numbers of contacts. Some healthcare systems send reminders to people vaccinated in previous years reminding them to be vaccinated for the upcoming influenza season [32, 33]. Practically, this is an effective practice because past vaccination is a strong predictor of future willingness to be vaccinated, but this study shows that this healthcare intervention may have population-level benefits beyond that of simply increasing vaccine coverage. The benefits of revaccination should be weighed against the potential deleterious consequences of prior vaccination on vaccine effectiveness and, perhaps especially, the development of heterosubtypic immunity. The results of our study demonstrate that policy debates about repeated influenza vaccination and the related topic of universal vaccination should take into account disease ecology and, especially, herd immunity considerations, not just immunological and public health implementation considerations.

Fig. 5. (a) Estimated probability of first-season vaccination is constant regardless of degree (black \(\times\)). Nodes of higher degree are more likely to be infected during the first season epidemic and therefore more likely to have natural immunity (black circles, \(\bullet\)). Consequently, lower degree nodes are more likely to be susceptible prior to the second season epidemic (grey circles, \(\square\)). The probabilities shown here are calculated for the 0% revaccination level, but the qualitative patterns are similar across all revaccination rates. We note that this panel does not reflect the degree distribution of the network. (b) At higher revaccination rates, the mean degree of second-season susceptible nodes decreases. Here, the mean degree of susceptible nodes is normalized by the network’s mean degree. This Figure is based on results from 2000 simulated second-season large epidemics on a single 5000 node exponential random network with \(T_1 = 0.09\), \(T_2 = 0.18\), \(E = 1.0\), \(Q = 1.0\), and \(C = 0.25\).
METHODS

Defining revaccination

We define the rate of revaccination \( (r) \) as the proportion of vaccine recipients in one influenza season who are also vaccinated in the following season. The revaccination rate is easiest to conceptualize if populations are closed and the level of vaccine coverage is constant across both seasons. Under those conditions, as vaccine coverage approaches 100\%, the revaccination rate also converges to 100\%. However, if the overall vaccination coverage is \( \leq 50\% \), the range of theoretically possible revaccination rates is 0–100\%.

If vaccination were random with respect to previous vaccination status, the expected revaccination rate would be equal to the vaccination coverage. To account for this, we additionally define \( r' \) to be the excess revaccination rate, which measures revaccination beyond what is expected at random conditional on the coverage level,

\[
r' = \frac{r - C}{1 - C}
\]

where \( r \) is the absolute rate of revaccination and \( C \) is the vaccine coverage. For almost all of our analyses we will simply use \( r \), because vaccination coverage will be held constant; the excess revaccination rate is used only for empirical estimation of revaccination.

Population model

We simulated epidemics on computationally generated contact networks. Computationally generated theoretical networks allow us to systematically study the epidemiological consequences of network structure. The network structure used in this study is an exponential random network, with the number of contacts per individual (i.e. degree) sampled from a geometric distribution, and connected randomly. We assume an average degree of 10 contacts per individual and a network size of 5000 nodes. (The impact of these choices is studied in the sensitivity analyses.) Bansal et al. [34] found that contact networks derived from empirical data correspond more closely to exponential random network structures than other common network types.

Epidemiological two-season model and vaccination

We model first-season vaccination with single doses of influenza vaccine by removing select individuals from the network. Individuals to be vaccinated are chosen randomly, and the size of the population to be vaccinated (and thus fully protected against influenza) is \( C*E \), where \( C \) is the vaccine coverage rate, and \( E \) is the vaccine efficacy. We call the set of individuals who are vaccinated in the first season, \( V_1 \), and note that these individuals are only protected for the first season (as influenza vaccine-induced immunity is temporary).

To model the first-season outbreak, we perform Monte Carlo simulations for a susceptible–infected–recovered (SIR) epidemic model with a single initial infected case and per-contact transmissibility, \( T_1 \), on all susceptible individuals in the networks specified above. Once infected, a node cannot be reinfected during the same season, and unlike with vaccination, will have resistance to infection during the subsequent season (natural immunity). This is a reasonable assumption because natural immunity is thought to induce a stronger, longer lasting immune response than vaccines, and provide better cross-protection across strains [12, 35–39].
Second-season vaccination is modelled similarly, except the identity of vaccinated individuals is no longer completely random. Based on the revaccination rate, \( r \), a proportion \( r \) of the vaccinated group \( (V_1) \) is vaccinated first. The remaining vaccine supply \((C - rV_1)\) is distributed randomly in the rest of the population.

The second-season outbreak is also modelled with a Monte Carlo SIR model, and an independent transmissibility \( T_2 \). In our simulations, \( T_2 \) is chosen to be greater than \( T_1 \) to ensure a comparable \( R_0 \) across both seasons (as \( R_0 \) is a function of both transmission probability and contact structure in this framework).

Infection in the second season is allowed in all susceptible individuals (that is, those individuals who do not have natural immunity from the first season and those who have not been vaccinated immediately prior to the second season). Second-season outbreaks are only considered in cases when a large epidemic occurs in the first season. The model assumes constant demography and constant network structure over the course of the two seasons. Public health burden is measured in terms of the proportion of the population infected in the event that there is a large epidemic in the second season.

### Universal vs. preferential vaccination

To consider the effect of susceptible population size on revaccination, we consider two models of second-season vaccination. One model—universal vaccination—follows the method outlined in the previous section, in which vaccine doses not used for revaccination are randomly administered to any individuals not vaccinated for the first season, including both naturally immune and never vaccinated or infected individuals. An alternative model—preferential vaccination—still implements revaccination as before, but the remaining doses are administered to individuals without natural immunity from the first season. (While this approach may not be realistic as individuals who are infected with influenza in a previous season might be more motivated to be vaccinated in a subsequent season, it provides a useful model for comparison.) When revaccination is complete \((r = 100\%)\), no individuals are vaccinated for the first time prior to the second season and, as such, the two models are functionally identical. Figure 3a confirms that under the preferential vaccination scenario, the proportion of all individuals who are susceptible prior to the second season does not change even as the revaccination rate changes. This is as expected, because under the preferential vaccination scenario, the number of susceptible individuals is simply the total number of individuals in the network minus the number of individuals with natural immunity from the first season and minus the number of individuals vaccinated for the second season.

### Realistic parameters

In the robustness analysis on the Vancouver urban network [25, 29], we divide the population into four age groups (0–4, 5–18, 19–64, ≥65 years). The vaccine efficacies for each of these age groups were 60%, 60%, 70%, and 50%, respectively, and were primarily based on clinical trials of influenza vaccines and meta-analyses thereof [3, 40–46]. We assume that vaccine efficacy in the second season is independent of first-season vaccination status. We also implement two vaccine-coverage scenarios. For a scenario based on the 2011/2012 influenza season in the United States, the age-specific vaccine coverage levels are 55%, 45%, 40%, and 70%, respectively [47]; for a scenario based on coverage levels from 2006 in the United States, age-specific vaccine coverage levels are 33%, 16%, 21%, and 65%, respectively [48, 49]. Revaccination rates are applied to each age group such that the excess revaccination is equal across age groups (i.e. differences in vaccine coverage are taken into account). While the relationship between immune response and future protection is not well quantified, the efficacy of natural immunity, \( Q \), for all age groups is assumed to be 80% [35, 38, 50, 51]. In this case, natural immunity is implemented in a manner similar to vaccination, so that 80% of those infected in the first season are assumed to be fully protected against infection, while the remaining 20% are not protected at all.

We reviewed the literature for empirical rates of revaccinations. Rates likely vary between populations, perhaps depending on factors such as access to vaccines and the overall rate of vaccination in the population. Data from a study of Medicare beneficiaries [32] indicates a revaccination rate of 93.4% between the 1998/1999 and 1999/2000 influenza seasons with a 70% vaccine coverage rate; while Uddin et al. [52] surveyed college students and found a revaccination rate between the 2006/2007 and 2007/2008 seasons of 58.5% with an average coverage rate of 15.65%. Last, based on data reported in a large study of people aged ≥65 years in the Netherlands, we estimated rates of revaccination generally between 80% and 90% [15].
The methods for the sensitivity analyses are described in the Supplementary material.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268815002253.

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DECLARATION OF INTEREST

None.

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