Optimal design of studies of influenza transmission in households. I: Case-ascertained studies

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SUMMARY

Case-ascertained household transmission studies, in which households including an 'index case' are recruited and followed up, are invaluable to understanding the epidemiology of influenza. We used a simulation approach parameterized with data from household transmission studies to evaluate alternative study designs. We compared studies that relied on self-reported illness in household contacts *vs.* studies that used home visits to collect swab specimens for virological confirmation of secondary infections, allowing for the trade-off between sample size *vs.* intensity of follow-up given a fixed budget. For studies estimating the secondary attack proportion, 2–3 follow-up visits with specimens collected from all members regardless of illness were optimal. However, for studies comparing secondary attack proportions between two or more groups, such as controlled intervention studies, designs with reactive home visits following illness reports in contacts were most powerful, while a design with one home visit optimally timed also performed well.

Key words: Epidemiology, virus infection.

INTRODUCTION

Influenza virus is associated with a substantial global burden of morbidity and mortality, yet many characteristics of the disease are poorly understood including transmissibility and its relationships with viral shedding during infection, factors affecting infectiousness and immunity, and the effectiveness of interventions to reduce transmission. Households are important in influenza epidemiology [1], and it has been estimated that around a third of all influenza transmission occurs in households [2]. Historically, household studies have provided invaluable insights into influenza epidemiology [3], while recent household studies have investigated the effectiveness of antiviral treatment and prophylaxis [4–8], hand hygiene [9–11], face masks [10–13], transmissibility of seasonal influenza [14] and 2009 pandemic influenza A(H1N1) [15–22].

There are two main types of design for household studies. A cohort of initially uninfected households can be recruited and then followed up through periods of influenza activity [3, 23]. While this is regarded as the gold standard for influenza household studies, this design can be extremely resource-intensive because the expected number of households in which an infection occurs is relatively small. Alternatively, households can be enrolled in a study once influenza infection is identified in one member (an 'index' case), and followed up to observe secondary infections. The latter design is termed a case-ascertained design [24],

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and is the focus of this paper. Case-ascertained studies are believed to be the most efficient method of assessing secondary transmission of influenza because smaller sample sizes are required to observe an equivalent number of secondary infections compared to a cohort study. In case-ascertained studies, influenza transmission is typically measured via the secondary attack proportion (SAP), defined as the proportion of household contacts that are infected with influenza virus from the index case [15].

While some case-ascertained studies rely entirely on self-reports of symptoms and signs associated with acute respiratory illnesses [12–17], repeated home visits can be arranged to collect specimens and allow virological confirmation of influenza virus infections [10, 11, 19–22]. Since secondary cases shed detectable virus for 3–5 days after illness onset it is important to consider the number and timing of visits in order to maximize the number of secondary cases that can be confirmed virologically. However, home visits can be associated with significant costs and there is a resource trade-off between the number of home visits per household vs. the total number of households that can be recruited given a fixed total budget for fieldwork.

Selecting an appropriate study design is part of Good Clinical Practice and use of suboptimal designs could squander research funding and put participants at unnecessary risk and inconvenience. In this paper we evaluate which study designs make the most cost-effective use of resources for accurately and robustly estimating the SAP in a transmission study, and for maximizing statistical power in a comparative study.

METHODS

As a basic scenario, we considered case-ascertained studies of household transmission of influenza virus where index cases are recruited after presentation at a study clinic. In this scenario, relatively inexpensive point-of-care rapid tests which are able to detect influenza virus infection with moderate sensitivity and high specificity [25] are used to identify index cases with influenza. For those index cases with a positive rapid test result, an initial home visit is conducted as soon as possible to collect laboratory specimens from all household contacts to determine whether there are any co-primary cases. If a co-primary case is found, the family are not enrolled in the study [10, 26]. A series of additional home visits might be conducted at later dates to collect further specimens for virological confirmation of secondary cases. Symptom diaries can also be provided to household members to permit self-reporting of signs and symptoms associated with acute respiratory illness (ARI). We define ARI as the presence of two of the following symptoms: fever ($\geqslant 37 \cdot 8\ °C$), cough, headache, sore throat, or myalgia, and influenza-like illness (ILI) as temperature ($\geqslant 37 \cdot 8\ °C$) plus cough or sore throat [10, 21]. ILI is a more specific but less sensitive indicator of acute influenza virus infection than ARI [10, 21, 27].

Transmission study

In a transmission study primary interest is in estimating the household SAP. If home visits are not feasible logistically, studies based on self-reported secondary cases can be conducted [14, 15]. However, no clinical definition of influenza has high sensitivity and high specificity and therefore estimates of SAP based on clinical definitions may not accurately or robustly measure the true SAP [10, 21, 27]. If feasible, home visits are an important component of a design allowing virological confirmation of secondary cases. It is also possible to restrict home visits to households where contacts report illness [5–7]. Since sample size calculations without any home visits are straightforward using standard methods, here we focus on comparing transmission studies with one or more follow-up visits vs. the use of ILI or ARI in contacts to trigger home visits, or clinical outcome definitions alone.

Comparative study

In a typical comparative study, one or more active intervention is compared with a control. In these studies primary interest is usually in comparing the effectiveness of interventions on household SAPs with measures such as the incidence rate ratio, relative risk, or odds ratio, and studies are designed that allow moderate to high power for detection of intervention effects. In this scenario virological confirmation of secondary cases might be less important since intervention effects might still be identifiable in comparisons of clinical outcomes between arms. We compare two-arm comparative studies with no follow-up visits, visits triggered by ARI or ILI, or one or more follow-up visits regardless of illness.

Data sources

To permit simulation of alternative study designs, some basic parameters are required which characterize

Table 1. *Epidemiological parameters*

Parameter	Value	Source
Serial interval for influenza	Weibull distribution with mean 3·2 days	[21]
SAP control group	10%	Assumed
SAP intervention group	5%, 7·5%	Assumed
Total number of people per household	4	Assumed
Specificity of RT–PCR	100%	Assumed
Sensitivity of ARI compared to virologically confirmed infection	68%	[10]
Specificity of ARI compared to virologically confirmed infection	86%	[10]
Sensitivity of ILI compared to virologically confirmed infection	40%	[10]
Specificity of ILI compared to virologically confirmed infection	98%	[10]
Cost of recruiting an index case	US$ 360	(B. J. Cowling, personal communication)
Cost of a home visit	US$ 120	(B. J. Cowling, personal communication)

SAP, Secondary attack proportion; ARI, acute respiratory illness; ILI, influenza-like illness.

influenza transmission in households (Table 1). We assumed that in addition to the index case there are three additional household members. We assumed that an index case is seen in a clinic and a subsequent home visit confirms that the remaining household members are negative within 24 h of symptom onset of the index case. We also assumed that there is no within-household tertiary transmission because tertiary transmission is relatively rare and should have little effect on the estimation of SAP.

Costs are also required, since an optimal design must trade-off the total sample size with the number of follow-up visits. We specified the recruitment and enrolment costs per household as C_E and the cost of a home visit as C_V. In a previous study in Hong Kong, C_E was three times as much as C_V (Table 1). In sensitivity analyses we also considered ratios of 2:1 and 4:1. With a fixed fieldwork budget of C, the total number of households n that can be recruited depends on the number of follow-up home visits v and can be calculated with the formula $n = C/(C_E + vC_V)$.

Statistical analysis

We re-analysed data on viral shedding during illness associated with natural influenza virus infection [10, 28]. The probability of virological confirmation by RT–PCR was estimated using logistic regression with a cubic spline term for time since illness onset.

For transmission studies, accurately estimating the SAP is of primary importance. Consequently, as a design with only one home visit will miss more infections than those with more home visits, studies with more home visits are less biased than those with fewer home visits. However, this should come at the cost of greater variance in parameter estimates due to the reduced sample size. Therefore the choice of more home visits relative to decreased overall sample size should represent a bias-variance trade-off. We examined the overall efficiency of estimation by estimating the mean squared error (MSE) and mean absolute error (MAE) of the SAP under each design. The MSE and MAE are both measures of the expected difference between the estimate of a parameter and the actual parameter value, and a smaller MSE or MAE indicates greater precision and less bias.

For comparative studies, we estimated the power of each potential design to detect a specific treatment effect in terms of a reduction in the estimated SAP in the intervention *vs.* the control group, expressed as an odds ratio. To calculate power, a logistic generalized estimating equation [29] accounting for within-family correlations was fitted to the simulated data. The statistical power was estimated as the number of simulated datasets in which the intervention effect was identified at a significance level of $P \leqslant 0.05$.

Due to the nonlinearities in transmission dynamics we used a simulation approach to compare alternative study design variants [30]. For each study design variant we used a Monte Carlo approach to simulate a set of 2500 datasets. The MSE and MAE or power of each variant were evaluated by statistical analysis of the set of 2500 simulated datasets and compared across design variants. Further technical details are provided in the Supplementary Appendix (available online).
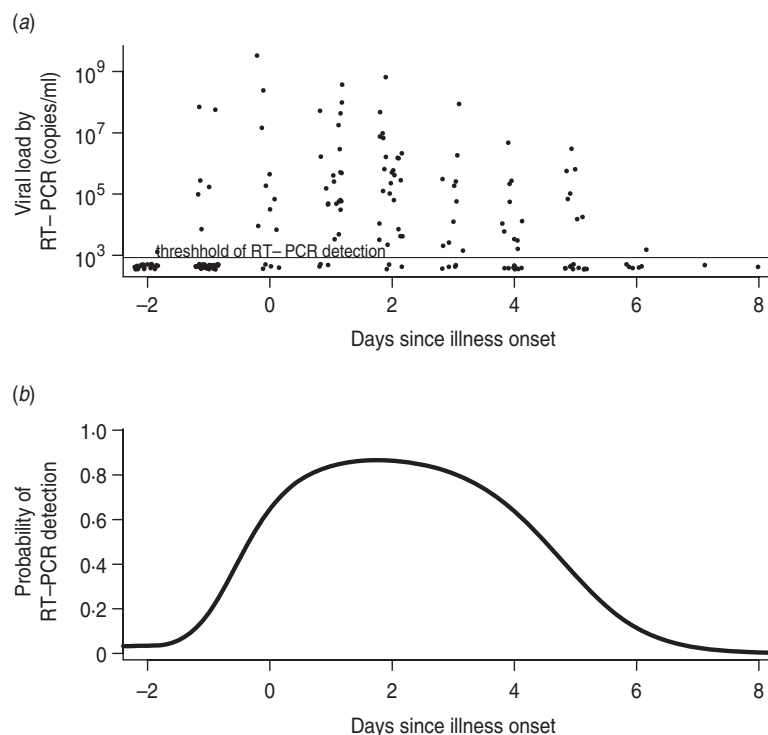
Fig. 1. (a) Intensity of viral shedding associated with influenza A virus infections, and (b) probability of virological confirmation of influenza A virus infection in a subject by day of collection of a nose and throat swab. (Based on data from Lau *et al.* [28].)

Sensitivity analyses

In addition to examining the sensitivity of our results to costs as described above, we also examined how a shorter serial interval of mean 2·6 days [15, 31, 32] or a longer serial interval of mean 3·6 days [33] would affect our results.

RESULTS

We parameterized our simulation model using results from the literature and analyses of data from a household study (Table 1) [10, 28]. In a secondary analysis of data from a field study, we estimated that the probability of virological confirmation of infection was highest when specimens were collected within 1–3 days of illness onset (Fig. 1).

Transmission studies

We examined the optimal timing of home visits for a transmission study with one or with two home visits. We found that the optimal timing was 6 days from ARI onset in the index case for a one home-visit design, 5 and 7 days from ARI onset in the index case for a two-home-visit design and 3, 5, and 7 days for a three-home-visit design. We found that as the study budget increased, designs with two and then three home visits led to the lowest MSE and MAE, and this was robust to differences in the $C_E:C_V$ ratio (Fig. 2). As total study budget increases, designs with four, five, and even more home visits will become optimal in terms of reducing the MSE (data not shown). We also found that studies with more home visits performed substantially better in terms of MSE and MAE than those using only self-reported clinical outcomes of ILI and ARI. Using ILI to trigger home visits appeared to be as accurate as conducting home visits for all families regardless of illness.

Comparative studies

For a comparative study we found that the optimal visit timing was 6 days from ARI onset in the index case for a one-home-visit design, 5 and 7 days from ARI onset in the index case for a two-home-visit design (Fig. 3) and 3, 5, and 7 days for a three-home-visit design. For the comparative study, a design in which a home visit occurs after being triggered by ARI in a family member was most powerful.
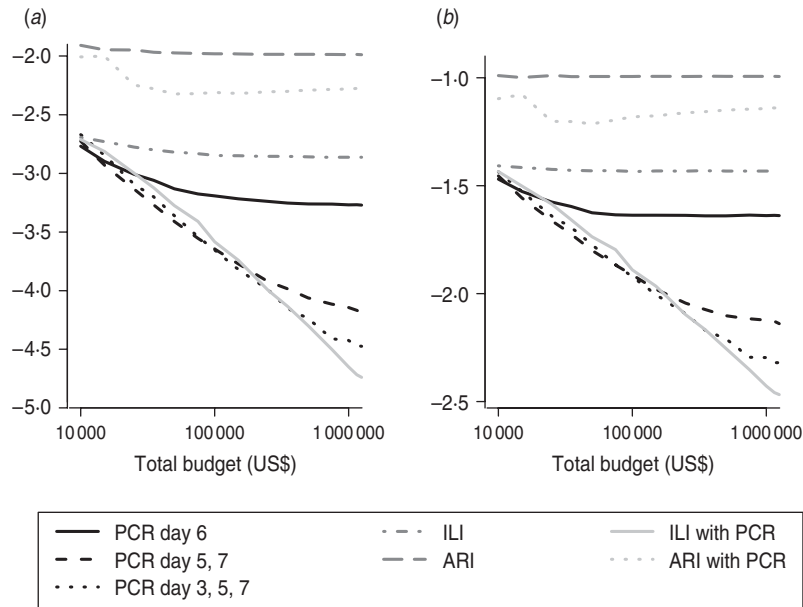
Fig. 2. (*a*) Estimated mean squared error (MSE) and (*b*) mean absolute error (MAE) of the secondary attack proportion for varying transmission studies. For a given budget, lower values of MSE and MAE indicate better designs. The black lines represent study designs involving home visits with subsequent virological confirmation for all families on the specified days, the medium grey lines represent self-report of influenza-like illness (ILI) or acute respiratory illness (ARI) without virological confirmation, and the light grey lines represent a home visit with subsequent virological confirmation when an ARI or ILI is reported within a family.
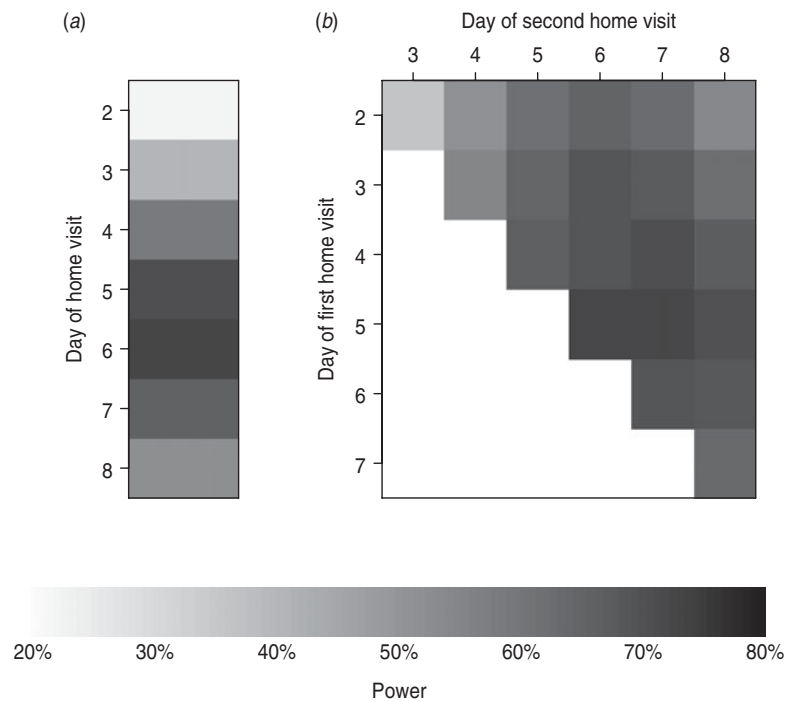

Fig. 3. Power of comparative study designs with alternative home visit schedules by days since acute respiratory illness onset in the index case for (*a*) studies with one home visit and (*b*) studies with two home visits.

In designs where visits were conducted to swab all participants regardless of illness, a design with one home visit on day 6 was most powerful to detect an overall difference in SAP between the control and intervention groups (Fig. 4). However, differences in power between designs with one home visit and
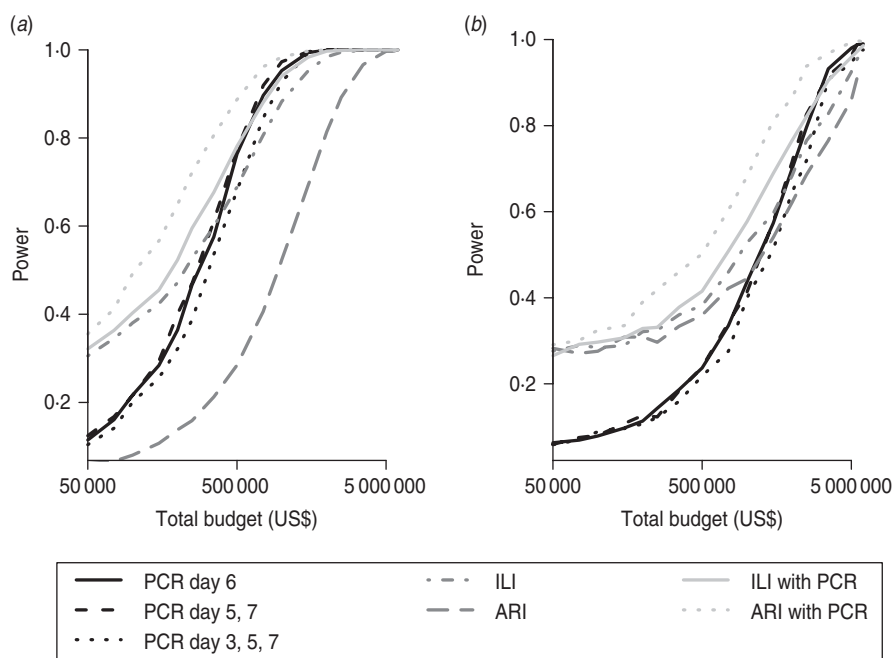
Fig. 4. Power of alternative designs for comparative studies with respect to (*a*) an odds ratio of 0·67 (true relative risk of 0·7) and (*b*) an odds ratio 0·84 (true relative risk of 0·85). The black lines represent home visits with subsequent virological confirmation for all families on the specified days, the medium grey lines represent self-report of influenza-like illness (ILI) or acute respiratory illness (ARI) without virological confirmation and the light grey lines represent a home visit with subsequent virological confirmation triggered by reports of ARI or ILI by a household contact.

multiple home visits were very small, particularly as the cost of home visits decreased relative to the cost of enrolment. Designs with home visits outperformed those relying solely on the self-reported clinical outcomes of ARI and ILI. Finally, studies based on ILI outcome had higher power than those based on ARI.

Sensitivity analyses

Using a serial interval with mean 2·6 or 3·6 days resulted in the optimal timing of visits being shifted slightly earlier or later, respectively, but the patterns in terms of the optimal strategy for visits remained similar. For example, for a comparative design the optimal timing with a serial interval with mean 2·6 days was day 5 for one visit and days 4 and 6 after illness onset for two visits, while for a serial interval with mean 3·6 days it was 6 days for one visit and 5 and 7 days after illness onset for two visits.

DISCUSSION

Careful consideration is necessary when planning case-ascertained studies of influenza transmission. If the aim of a study is to assess the household SAP, then conducting more than one home visit in

most circumstances would be optimal (Fig. 2). In the case of a study comparing SAPs between two or more groups, such as a controlled trial, the optimal design would be to have one home visit on day 6. However, the differences in power between designs with one visit or multiple visits were relatively small (Fig. 4). Our results would suggest that given a reasonable cost per home visit, the use of home visits is a cost-effective strategy compared to relying solely on clinical diagnosis of influenza from self-report data. When resources for home visits are limited, ARI or preferably ILI could be used to trigger home visits (Fig. 3) and this method performs well. In comparative studies based on clinical outcomes alone, ILI was associated with greater power than ARI because of the very high specificity of ILI case definition.

Despite the number of clinical and epidemiological studies using longitudinal (repeated-measure) designs, there is a paucity of literature discussing the optimal choice of the number of repeated measurements [34]. The majority of work considering the design of randomized controlled trials with repeated measurements treats the number of repeated measurements as a fixed and known aspect of design [35, 36]. Of the few studies which have treated the number of repeated measurements as a variable to be optimized, Winkens

et al. [37] consider the optimal number of repeated measurements when treatment outcomes are linearly divergent while Cook *et al.* [38] consider the optimal choice of measurements in epidemic processes. Those approaches are not directly applicable to the scenarios described in the present study because the probability of influenza infection and subsequent detection is highly nonlinear with regard to time since infection (Fig. 1). While our work is specific to household transmission of influenza virus, the results may generally translate to similar studies of other respiratory viruses such as rhinovirus and respiratory syncytial virus, provided that corrections are made for their specific natural history [39].

Throughout all simulations the use of ARI or ILI to trigger home visits performed as well or better than the use of home visits for all families. One caveat is that in that scenario some illnesses might not be reported leading to missed infections, while symptom diaries might be completed more meticulously if household members knew that home visits would be conducted regardless of illness. One other possibility is to invite participants to swab themselves during follow-up, thereby reducing the cost of a home visit but maintaining a virological outcome. We did not include self-swabbing in our analyses as we could not find any data on the sensitivity of self-swabbing compared to swabs collected by experts.

The optimal timing of home visits depends on the serial interval, which determines when infected secondary cases will on average have illness onset, and also depends on the probability of virological confirmation of infection by day since illness onset. In a novel analysis of secondary data we showed that the probability of virological confirmation of an infection is highest if swabs are taken on days 1–3 of illness (Fig. 1). While we compared study designs in terms of time since index case illness onset, in some protocols timing is specified as time from enrolment of a family and if enrolment is completed on average 24 h or 48 h after symptom onset, then 1 or 2 days should be subtracted to calculate optimal timing of visits after enrolment. Figure 3 shows that home-visit timings of around 4–7 days after symptom onset work reasonably well. While the optimal timing may seem late compared to the mean serial interval, it should be noted that later follow-up visits allow the detection of secondary cases with earlier infection (who are still shedding detectable virus) as well as those with later infection.

Our study has practical limitations when considering its application to the planning of future studies.

First, our results on the optimal timing of visits depend on estimates of the serial interval and the duration of detectable viral shedding. We have focused on studies of influenza A epidemiology. Studies including influenza B should consider how differences in viral shedding [28, 40] and other epidemiological characteristics might affect these conclusions. Second, future improvements in the cost or accuracy of laboratory methods could change the optimal number of home visits. Third, we would caution that although it appears diagnosis of influenza based on self-report provides less power than influenza detection through home visits and subsequent RT–PCR, clinical influenza may be the only feasible outcome measure in some settings, and an important primary outcome in studies such as antiviral prophylaxis if the aim were to reduce illness in household contacts rather than prevent infection. We incorporated alternative assumptions about the relative costs of enrolment and follow-up, but other logistical considerations may play a role in study design. For example, if only one clinic is available for recruitment then a study with many home visits and a smaller sample size might be preferred, but the reverse could be true if community nurses capable of conducting home visits were in short supply. If paired sera were available from baseline (pre-infection) and convalescence (21–28 days after infection), comparison of antibody titres could provide serological confirmation of infection, although it can be challenging to obtain sera from participants in community studies. Finally, Yang *et al.* [24] noted that in simulation studies direct randomization of family members rather than cluster randomization of families would be more powerful. However, this is not always possible, for example in studies where non-pharmaceutical interventions or antiviral treatments are given to the index case to attempt to reduce onwards transmission.

Despite these potential limitations, our results should serve as useful guidelines for researchers planning future case-ascertained studies of influenza transmission and control. Our findings illustrate that if feasible, collection of specimens for virological testing can be a cost-effective use of resources.

NOTE

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/hyg).

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DECLARATION OF INTEREST

None.

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