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Entry screening to delay local transmission of 2009 pandemic influenza A (H1N1)

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Abstract

Background: After the WHO issued the global alert for 2009 pandemic influenza A (H1N1), many national health agencies began to screen travelers on entry in airports, ports and border crossings to try to delay local transmission.

Methods: We reviewed entry screening policies adopted by different nations and ascertained dates of official report of the first laboratory-confirmed imported H1N1 case and the first laboratory-confirmed untraceable or 'local' H1N1 case.

Results: Implementation of entry screening policies was associated with on average additional 7-12 day delays in local transmission compared to nations that did not implement entry screening, with lower bounds of 95% confidence intervals consistent with no additional delays and upper bounds extending to 20-30 day additional delays.

Conclusions: Entry screening may lead to short-term delays in local transmission of a novel strain of influenza virus. The resources required for implementation should be balanced against the expected benefits of entry screening.

Background

Pandemic influenza A (H1N1) virus emerged in Mexico in early 2009. Rapid global spread was primarily associated with air travel [1]. As the World Health Organization (WHO) raised their pandemic alert level to 4 and then 5 in April, national health agencies across the world activated their pandemic plans. Following guidance by WHO, many authorities began to screen travelers on entry in airports, ports and border crossings, isolate suspected or confirmed cases, and quarantine their close contacts [2]. Exit screening was not implemented by source nations. Modeling studies suggested that entry screening could not prevent introduction but might be able to delay local epidemics by a few weeks [3-6]. Entry screening and quarantine did not substantially delay introductions in previous pandemics [7]. We reviewed entry screening policies adopted by different nations and estimated the range of delays in local epidemics associated with entry screening.

Methods

To explore potential delays in local H1N1 transmission associated with entry screening, we ascertained dates of official report of the first laboratory-confirmed imported H1N1 case and the first laboratory-confirmed untraceable or 'local' H1N1 case (i.e. a case not otherwise epidemiologically linked with international travel, contact with an imported case or their secondary infectees) and the interval between these two events. We calculated the additional delays associated with entry screening tools versus the observed delays in nations that did not screen. Since the data did not follow a normal distribution we estimated 95% confidence intervals for these differences using bootstrapping, which is a resampling technique suitable for statistical inference in small sample sizes with non-normal distributions [8]. We based each bootstrap confidence interval on 1,000 resamples. Statistical analyses were conducted using R (R Development Core Team, Vienna, Austria) [9].

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The study was conducted between July 13 and August 22, 2009. The methods of entry screening employed were identified by review of official national health ministry websites and the media, and Google searches in English using queries of the form ("<country name>" AND ("influenza" OR "H1N1" OR "swine flu" OR "pandemic" OR "Mexican flu")). We included each nation that had notified more than 100 confirmed H1N1 cases to the World Health Organization by July 6, 2009, except Mexico and the United States where local transmission occurred prior to the WHO global alert. To determine the date of first imported case and first local case the search queries were extended accordingly. Queries were translated by Google language tools http://www.google.com/language_tools and Babelfish http://babelfish.yahoo.com to local official languages and searches were repeated to further increase our scope. We searched for websites in languages including Chinese, Dutch, French, German, Greek, Hebrew, Japanese, Korean, Portuguese, Spanish and Thai.

Results

We identified 35 nations that had reported more than 100 confirmed H1N1 cases to the World Health Organization by July 6 (we included Hong Kong separately from mainland China as it has separate administration) (Additional file 1). The date of the first untraceable local case could not be determined for 9/35 of the nations. Further details and web links to relevant reports and original data sources are available from the corresponding author on request.

We identified four broad approaches to entry screening. First, temperature checks were performed onboard aircraft prior to disembarkation. Second, health declaration forms were collected from every traveler or all travelers from countries identified with confirmed H1N1 cases. Third, arriving travelers were observed by alert staff for influenza symptoms (e.g. cough). Fourth, travelers were scanned for elevated body temperature by thermal scanners. In the majority of countries screening was implemented by May 1, 2009 although we were unable to determine whether there were any substantial changes in screening protocols after commencement of screening but before confirmation of the first local case.

Because of stochasticity (i.e. chance variations in the occurrence of secondary transmission due to small number of cases initially), the single observed interval between the confirmation of the first imported case and the first local case in a given country is not easily interpretable. We examined patterns in aggregated data expecting that errors due to stochasticity should tend to average out in comparisons between groups of countries using similar tools. Two nations (China and Japan) implemented all four tools. Five nations did not implement any of the four. Table 1 shows the intervals between confirmations of first imported cases and first local cases, categorized by entry screening tools. Overall, implementation of the four tools alone or in combination were associated with on average additional 7-12 day delays in local transmission compared to nations that did not implement entry screening, with lower bounds of 95% confidence intervals consistent with no additional delays and upper bounds extending to 20-30 day additional delays (Table 1). Dates of illness onset were available for the first imported cases in 11/26 nations and the first local cases in 4/26 nations, and mean delays were similar in that subset (data not shown).

Discussion

Our results suggest that entry screening did not lead to substantial delays in local H1N1 transmission (Table 1). This empirical study is consistent with theoretical results from previous modeling studies [3-6] and findings from previous pandemics [7]. While longer delays in local transmission to the summer in countries in the Northern hemisphere could have substantially aided pandemic mitigation, due to seasonal factors [3] and school vacations [10,11] leading to lower peak attack rates [12], the observed delays in the present pandemic

Table 1 Use of alternative entry screening approaches and intervals between official confirmation of first imported pandemic influenza A (H1N1) case and official confirmation of first untraceable local case for 26 nations with more than 100 confirmed cases by July 6, 2009.

Screening approaches used	n (%)	Median interval, days (inter-quartile range)	Mean interval, days	Mean difference in intervals compared to no screening (95% CI)*
No screening	5 (19%)	22 (0, 22)	14	
1- Medical checks before disembarkation	2 (8%)	21 (14, 28)	21	7 (-14, 30)
2- Health declaration forms	11 (42%)	22 (13, 34)	23	9 (-4, 24)
3- Symptom screening	13 (50%)	33 (7, 41)	26	12 (-2, 27)
4- Thermal scanners	13 (50%)	22 (7, 33)	21	7 (-6, 23)
2 OR 3 OR 4	21 (81%)	22 (7, 35)	23	9 (-3, 22)
2 AND 3 AND 4	6 (23%)	23 (9, 35)	22	7 (-9, 25)

*95% confidence intervals estimated by bootstrapping with 1,000 resamples.

suggest entry screening provided around 1-2 weeks of additional time for preparation and planning.

While our study focused on the impact of entry screening, some nations also implemented other containment and mitigation measures, such as isolation of suspected or confirmed cases, quarantine of their contacts with or without antiviral chemoprophylaxis, school closures or other social distancing measures, and public health campaigns to improve hygiene. Most nations enhanced their influenza surveillance. If countries that expended greater effort into entry screening also had more effective containment and mitigation measures in the general population, these might have led us to overestimate the effect of entry screening. Conversely, if countries that expanded greater effort into entry screening also tended to have better influenza surveillance and were able to identify local transmission earlier, we may have underestimated the effect of entry screening. Other differences between countries in laboratory capacity and availability of public health resources may also have confounded our evaluation, and all of these factors are limitations of our study.

Previous mathematical modeling studies have questioned the value of entry screening, since it could only delay rather than prevent local epidemics [3-6]. However, most models assumed that source countries would conduct exit screening and infectious cases would not travel [3-6]. In such a scenario it is not surprising that entry screening would add little benefit, since most journeys are shorter than the average 1.5-2 day incubation period for influenza A virus infections [5,13]. Screening is unlikely to identify 100% of ill travelers, while some might use antipyretics to reduce a fever prior to passing through thermal scanners, or fail to report symptoms on declaration forms. Many individuals with subclinical or asymptomatic illness would not be identified, and could initiate outbreaks after arrival [14]. In Hong Kong, only one third of confirmed imported H1N1 cases were identified through screening on entry to Hong Kong, the majority of imported cases were identified through the local health care system after arrival (T. Tsang, personal communication). A similar experience has been reported in Singapore [15]. Nevertheless, entry screening could act as a deterrent to traveling when ill or lead to other indirect benefits such as improving public awareness of the pandemic.

For entry screening to be successfully employed, substantial resources are required to identify the small fraction of travelers who may have H1N1 infection [16]. Further resources may be needed to isolate identified cases, and trace and quarantine close contacts. An important caveat is that a delay in inevitable local transmission of a pandemic virus may not be desirable if it would defer local transmission into a season associated with higher transmissibility such as the winter in temperate regions [12], or if it led to importation and local transmission of antiviral resistant strains [17].

In addition to the caveats on potential confounding by resource availability, competing interventions, and other differences discussed above, there are a number of further limitations to our study. First, identification, confirmation and notification of H1N1 cases is unlikely to have been perfect given the mild and self-limiting nature of most infections, and dates of importation and local transmission that we report may lag behind the true events of interest. Nations that devoted greater resources to entry screening may have identified imported cases earlier. Secondly, we have not considered the size of local epidemics, or how the degree of connectivity with source regions (for example the number of travelers per day) might relate to time delays between imported and local cases. Thirdly, by focusing on nations with at least 100 confirmed cases by July 6, 2009 we may have excluded nations where entry screening was more effective in delaying local transmission, or excluded some nations with fewer resources available for surveillance and confirmation of local cases. Fourthly, while we searched for the dates of reporting of the first imported case and first local case, these dates may not have corresponded exactly to the dates of identification and confirmation of those cases, since in some cases delays may have occurred for various reasons including political considerations. Finally, we collected data from online sources including official government websites, and we have included the hyperlinks in Additional file 1, but information available on the internet could be inaccurate.

Conclusions

In conclusion, our results suggest that entry screening could delay local transmission for an additional 1-2 weeks. The uncertainty bound of the delay estimates ranged from no delay to 20-30 days delay. A delay of 1-2 weeks could be useful if the additional time permits more comprehensive planning and preparation for a local epidemic, or shortens the time required for other pandemic mitigation measures such as school closures to be sustained. However the benefits of local screening should be balanced against the considerable resources required to implement screening [14]. Our empirical results are consistent with the modeling literature, and support the guidance from the World Health Organization that entry screening can only prevent local spread for a short period of time [14].

Additional file 1: Use of entry screening* and interval between confirmation of first imported pandemic influenza A (H1N1) case and confirmation of first untraceable local case

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Authors' contributions
BJC conceived of the study and drafted the manuscript. BJC, LLH, PW and HWCW participated in data collection. VJF conducted the statistical analyses. SR participated in interpreting the results. HN participated in planning the study and interpreting the results. All authors were involved in critical review and editing of the first draft, and subsequent revisions to the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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Quarantine for pandemic influenza control at the borders of small island nations

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Abstract

Background: Although border quarantine is included in many influenza pandemic plans, detailed guidelines have yet to be formulated, including considerations for the optimal quarantine length. Motivated by the situation of small island nations, which will probably experience the introduction of pandemic influenza via just one airport, we examined the potential effectiveness of quarantine as a border control measure.

Methods: Analysing the detailed epidemiologic characteristics of influenza, the effectiveness of quarantine at the borders of islands was modelled as the relative reduction of the risk of releasing infectious individuals into the community, explicitly accounting for the presence of asymptomatic infected individuals. The potential benefit of adding the use of rapid diagnostic testing to the quarantine process was also considered.

Results: We predict that 95% and 99% effectiveness in preventing the release of infectious individuals into the community could be achieved with quarantine periods of longer than 4.7 and 8.6 days, respectively. If rapid diagnostic testing is combined with quarantine, the lengths of quarantine to achieve 95% and 99% effectiveness could be shortened to 2.6 and 5.7 days, respectively. Sensitivity analysis revealed that quarantine alone for 8.7 days or quarantine for 5.7 days combined with using rapid diagnostic testing could prevent secondary transmissions caused by the released infectious individuals for a plausible range of prevalence at the source country (up to 10%) and for a modest number of incoming travellers (up to 8000 individuals).

Conclusion: Quarantine at the borders of island nations could contribute substantially to preventing the arrival of pandemic influenza (or at least delaying the arrival date). For small island nations we recommend consideration of quarantine alone for 9 days or quarantine for 6 days combined with using rapid diagnostic testing (if available).

Background

Strict maritime quarantine (with facility quarantine on land in some cases), appeared to effectively prevent the entry of the 1918–19 influenza pandemic into American Samoa and delayed its entry into mainland Australia, Tasmania and New Caledonia [1]. Quarantine measures during this pandemic also worked successfully in Yerba Buena, an island off San Francisco [2], and within parts of Iceland [3]. More generally, a systematic review has reported evidence that interventions that included quar-

antine (2 studies) and isolation (10 studies) were effective in containing respiratory virus epidemics [4]. An earlier review had suggested a limited use for quarantine but had focused on quarantine attempts in countries with porous land borders [5].

Since it appears that quarantine was successful in island settings from 1918–19, some Pacific island nations have included the option of border quarantine in their current influenza pandemic plans [6]. Theoretically, since small island nations will most likely experience introduction of pandemic influenza at just one airport or seaport alone, the use of border control would be one of the most important options to protect their communities from the pandemic. As an example, New Zealand consists of multiple islands and has a pandemic plan that includes significant detail about border control and quarantine [6,7]. In addition, border quarantine is also included in the pandemic plans of some European countries [8].

However, detailed guidelines for effective use of quarantine have yet to be formulated. One of the key questions among infectious disease specialists and public health practitioners is how to optimise the duration of quarantine to achieve a desired level of effectiveness. Presently, there is no universal proposal for quarantine period following exposure to pandemic influenza cases. Although the etymological root of quarantine originates from 13th century public health practices requiring incoming ships to remain in port for 40 days [9], quarantine in the present day refers to compulsory physical separation for a defined period, including restriction of movement, of healthy individuals who have been potentially exposed to an infectious disease [10]. Since the restriction of movement often involves legal and ethical constraints, because it limits the freedom of quarantined individuals [11], the optimal length of quarantine needs to be clarified using scientifically sound approaches.

To suggest the optimal length of quarantine for pandemic influenza, we need to consider the detailed epidemiologic characteristics of this disease including the presence of asymptomatic infection [12]. The present study aimed to assess the potential effectiveness of quarantine, suggest an optimal length, and examine its potential performance for small island nations.

Methods

Hypothetical setting

To clarify the optimal length of quarantine, we first consider a hypothetical setting where infected travellers are flying from a nation with an epidemic (somewhere in Asia, given the data on the origin of seasonal influenza [13]) to a disease-free small island nation (e.g., New Zealand or smaller South Pacific and Caribbean islands). Specifically, we consider a situation when the disease-free country is fortunate enough to be informed about the possible emergence of the influenza pandemic at the source, sufficiently in advance of its arrival to implement border control measures. Given that the possible emergence is still uncertain and very recent news, we assume that the disease-free island nation is not ready or willing to completely shut down all its airports, but that quarantine is immediately instituted at the border. Before closing all the airports we assume that the island nation still permits the arrival of 20 aircraft with a total of 8000 incoming individuals (i.e., each with 400 individuals including airline staff on board) who were potentially exposed to influenza at the source country or on the aircraft. For this population of travellers we explore the question – how long should we place them in quarantine?

We assume that all incoming individuals are placed into routine quarantine on arrival in the island nation and are monitored for onset of symptoms during the quarantine period. We also assume that all infected individuals who develop influenza symptoms are successfully detected (e.g., through self-report questionnaires, reporting by ground staff, specific interview assessment by trained health personnel and/or thermal scanning). The impact of imperfect detection on the effectiveness of quarantine is examined in the Appendix. Optimistically, symptomatic cases are assumed to be immediately isolated in a designated facility at symptom onset, and assumed not to result in any secondary transmissions [14]. Similarly, those who developed symptoms en-route are also assumed to be successfully isolated upon arrival (and we ignore these individuals in the following analyses as the detection is owing to the entry screening). We assume that quarantine security would be fully effective and that no secondary transmission would occur in the quarantine facility. Successful detection during quarantine relies largely on onset of influenza-like symptoms, but, as a possible option, we also consider adding rapid diagnostic testing to improve the sensitivity of case detection.

Epidemiologic characteristics of influenza

To theoretically and quantitatively examine the effectiveness of quarantine, we use several parameters describing the epidemiologic characteristics of seasonal influenza – which we then use for considering pandemic influenza. The most important of these characteristics is the cumulative distribution of the incubation period (i.e., the time from infection to onset) of length t, $F(t)$. The incubation period has been very useful in suggesting the optimal length of quarantine for many diseases [15], because arbitrarily taking the 95th or 99th percentile point as the quarantine period could ensure the absence of symptomatic infection with probability of 95% or 99% [12,16-21]. However, it is difficult to directly apply this concept to influenza [12], because the conditional probability, α, of developing symptomatic disease (given infection) has

been suggested to be 66.7% [22,23], and detection through quarantine is not relevant for asymptomatic infected individuals who account for the remaining 33.3%. Thus, we consider the effectiveness of quarantine as the reduction of the risk of introducing "infectious" individuals into the community and, thus, additionally use the cumulative distribution of the generation time (i.e., the time from infection of a primary case to infection of a secondary case by the primary case) of length t, $G(t)$. Further, to simulate the key ripple benefit of quarantine (the predicted number of secondary transmissions caused by released infectious individuals), we assume that the reproduction numbers of symptomatic (R_s) and asymptomatic cases (R_a), i.e., the average numbers of secondary transmissions caused by a single symptomatic case and an asymptomatic case are 2.0 and 1.0, respectively. The basic reproduction number, R_0, is therefore $\alpha R_s+(1-\alpha)R_a = 1.67$ which corresponds to an estimate in a previous study [24]. Moreover, the estimate is also within the estimated range of community transmission in another study which explored various historical data [25].

Distribution of the incubation period, which was assumed to follow a gamma distribution, was extracted from a published dataset [26]. Since the original data showed daily frequency of onset only, we fitted the cumulative distribution of the incubation period to the observed data, minimising the sum of squared errors. We did not identify more detailed data and note that the obtained frequency did not deviate much from outbreak data on an aircraft [27,28], a historical study of Spanish influenza [15,29], and from data in a published meta-analysis [22]. Similarly, the generation time was retrieved from a previous study of volunteers infected with influenza [22], which assumed that infectiousness is proportional to viral shedding, and we obtained the parameter estimates by minimising the sum of squared errors. A log-normal distribution was employed to model the generation time. Strictly speaking, the viral shedding curve alone does not inform the generation time, but our outcome measure (i.e., the probability of releasing infectious individuals) is reasonably analysed using virological data (as we are dealing with infectiousness), assuming that the frequency of contact is independent of time since infection. Furthermore, we favoured the use of this dataset as it would give a more conservative result since the right-tail is fatter than those assumed previously [30,31].

Effectiveness of quarantine

Although secondary transmission on aircraft is probably relatively rare due to the functioning of ventilation systems [32,33], a previous transmission event has been reported in this setting [27]. Therefore, we use arrival time as the latest time of possible infection (i.e., $t = 0$). In other words, we conservatively argue the quarantine period as if all infected incoming individuals experienced this infection upon arrival. In reality, earlier acquisition of infection would increase the probability of non-infection after quarantine and therefore increase the effectiveness of quarantine. Although our worst case scenario potentially overestimates the optimal length of quarantine, a more realistic scenario requires the exact time of infection for all incoming infected individuals, which is in principle impractical (see Appendix for more detailed insights into this issue).

We considered the effectiveness of quarantine, $\varepsilon(t)$, as a relative reduction of the risk of introducing infected individuals into the community as a function of time since infection t, i.e.,

$$\varepsilon(t) = 1 - \frac{r_1(t)}{r_0(t)} \quad (1)$$

where $r_1(t)$ and $r_0(t)$ are the risks of releasing infected individuals into a new community in the presence and absence of the quarantine measure, respectively. Since all infected individuals enter the community without quarantine, we assume $r_0(t) = 1$ for any t. If the risk in the presence of quarantine, $r_1(t)$, is regarded as the risk of releasing "symptomatic infected" individuals (regardless of infectiousness) after quarantine of length t, $r_1(t)$ is given by $1\text{-}F(t)$. Therefore, only the incubation period determines the effectiveness, i.e., $\varepsilon(t) = F(t)$, which has been the fundamental concept in previous studies [12,15-21]. However, we further consider the infectiousness for influenza, emphasising the importance of asymptomatic infection, because the proportion $100\times(1\text{-}\alpha)$ is as large as 33.3%. We thus regard the risk $r_1(t)$ as the probability of releasing "infectious" individuals into the community after quarantine of t days.

To comprehensively discuss this issue we decompose $r_1(t)$ into the sum of symptomatic and asymptomatic individuals (denoted by $r_{1s}(t)$ and $r_{1a}(t)$, respectively). For those who will eventually develop symptoms, the probability of release, $r_{1s}(t)$, is

$$r_{1s}(t) = \alpha(1 - F(t))(1 - G(t)) \quad (2)$$

where $F(t)$ and $G(t)$ are, respectively, the cumulative distributions of the incubation period and generation time. Because of the absence of adequate data, we assume independence between the incubation period and generation time, which most likely yields conservative estimates of the effectiveness (compared to that explicitly addressing dependence between these two distributions). For those who remained asymptomatic throughout the entire course of infection, the probability $r_{1a}(t)$ is

$$r_{1a}(t) = (1\text{-}\alpha)(1\text{-}G(t)) \quad (3)$$

because the incubation period is not relevant to the detection of asymptomatic infected individuals. Due to the absence of data, it should be noted that we assume that the length of generation time among asymptomatic individuals is identical to that among symptomatic cases, an assumption that has been used by others [24,25]. As the assumption adds an uncertainty to the model prediction, we examine the potential impact of differing generation times between symptomatic and asymptomatic infected individuals (see Appendix). Consequently, the effectiveness of quarantine, $\varepsilon(t)$, is given by subtracting $r_{1s}(t)$ and $r_{1a}(t)$ from 1: i.e.,

$$\varepsilon(t) = 1 - [\alpha(1 - F(t))(1 - G(t)) + (1 - \alpha)(1 - G(t))] \quad (4)$$

We further investigate the additional benefit of testing for the pandemic influenza virus using rapid diagnostic testing during quarantine. A key assumption made is that the currently available diagnostic tests would perform as well with the new pandemic strain of virus (and be supplied to the islands in time). We assume that the sensitivity (S_e) and specificity (S_p) of the rapid diagnostic test are 69.0% and 99.0%, respectively [34]. Since our effectiveness measure is conditioned on infected individuals, the risk of releasing infectious individuals in the presence of quarantine with use of rapid diagnostic testing is obtained by multiplying a factor ($1\text{-}S_e$) to $r_1(t)$ which represents a proportion of cases that are missed even following rapid diagnostic testing. Thus, we get the effectiveness $\varepsilon_d(t)$ as

$$\varepsilon_d(t) = 1 - (1 - S_e)[\alpha(1 - F(t))(1 - G(t)) + (1 - \alpha)(1 - G(t))] \quad (5)$$

Due to the absence of more detailed data, we assume that both the sensitivity and specificity of the rapid diagnostic test are independent of time since infection. Considering that the sensitivity may well decline in later stages of illness (by implicitly assuming that the diagnostic test is correlated with viral load), it should be noted that the results associated with equation (5) are probably most valid only for those in the early stage of illness (which is consistent with our particular interest in quarantine period). We stress that the estimated effectiveness $\varepsilon_d(t)$ for a long quarantine period (e.g., longer than 8 days) should be treated cautiously. Since the sensitivity S_e of asymptomatic infected individuals may be smaller than that among symptomatic cases (due to lower virus shedding titres among asymptomatic individuals), we examine the effectiveness of quarantine with differing S_e between symptomatic and asymptomatic infected individuals (see Appendix).

Sensitivity analysis and preventive performance

We also examined the sensitivity of our effectiveness measures (4) and (5) to different lengths of quarantine and prevalence levels at the source by means of simulations. First, the sensitivity was assessed using the number of released infectious individuals after quarantine of length t. We examined plausible prevalence levels of 1%, 5% and 10% at the source, which respectively indicate that there were 80, 400 and 800 infected individuals among a total of 8000 incoming individuals. The highest prevalence, 10%, may represent transmission events within an airport of the country of origin or on an aircraft. The analysis was made by randomly simulating the incubation period (F), the generation time (G), the presence of any symptoms (α) and the sensitivity of the rapid diagnostic test (S_e) where F and G randomly follow the assumed gamma and lognormal distributions, respectively. The two dichotomous variables (i.e., the presence of symptoms and sensitivity of the rapid diagnostic test) were randomly simulated with uniform distributions (i.e., drawing random real numbers from 0 to 1) and using cut-off points at $\alpha = 0.667$ and $S_e = 0.690$. The random sampling was performed for the number of infected individuals (80, 400 and 800 times) in each simulation, and the simulation was run 100 times for each length of quarantine and prevalence level. To show the ripple benefit, we also investigated the number of secondary transmissions caused by released infectious individuals. This estimate was achieved by further randomly simulating the numbers of symptomatic and asymptomatic secondary transmissions. Both numbers were assumed to follow Poisson distributions with mean $R_s(1\text{-}G(t_d))(1\text{-}F(t_d))$ and $R_a(1\text{-}G(t_d))$, respectively, for each of the released symptomatic and asymptomatic infectious individuals after the quarantine of length t_d days.

Finally, we examined the preventive performance of quarantine combined with rapid diagnostic testing. When the combination scheme is employed, those testing negative to the rapid diagnostic test following quarantine of length t would be the population of interest, as they are then released into the community. Let p be the prevalence level at the source ($0 \le p \le 1$). Among infected individuals (who account for $100p$% of the travellers), the fraction of those who are detected or lose infectiousness following quarantine of length t (i.e., true positives) is $(1\text{-}r_1(t))$. Of the remaining infected individuals $r_1(t)$, the fraction of those testing positive, $S_e r_1(t)$, to the rapid diagnostic test are placed into isolation and, thus, are added to the true positives. Consequently, the remaining fraction $(1\text{-}S_e)r_1(t)$ are false negatives and are released into the community (Figure 1). Among uninfected individuals (i.e., $100(1\text{-}p)$% of the travellers), the length of quarantine does not influence the preventive performance (because they are not infected and their quarantine is irrelevant to the loss of infectiousness). Thus, among the total number of incoming travellers, the fractions $(1\text{-}p)(1\text{-}S_p)$ and $(1\text{-}p)S_p$ will be testing positive (false positives) and negative (true negatives), respectively, to the rapid diagnostic test. Consequently, positive predictive value (PPV) of quarantine combined with rapid diagnostic testing is

$$PPV = \frac{p[1-(1-S_e)r_1(t)]}{p[1-(1-S_e)r_1(t)]+(1-p)(1-S_p)} \quad (6)$$

whereas negative predictive value (NPV) is

$$NPV = \frac{(1-p)S_p}{p(1-S_e)r_1(t)+(1-p)S_p} \quad (7)$$

PPV measures the preventive performance of quarantine policy to correctly place infected individuals in quarantine (or isolation) during their infectious period (i.e., how efficiently are we placing infectious individuals in the quarantine facility, among a total of those who are diagnosed as positive either by quarantine of length t or rapid diagnostic testing). NPV measures the preventive performance of the release policy (i.e., how large is the fraction of true negatives among a total of those who are diagnosed as negative after the quarantine of length t and rapid diagnostic testing). We numerically computed both PPV and NPV for different prevalence levels (from 0–15%) and different lengths of quarantine (from 0 to 10 days). All analyses were made using the statistical software JMP ver. 7.0 (SAS Institute Inc., Cary, NC).

Results

Intrinsic dynamics of influenza

Figure 2 shows density functions of the incubation period and generation time. The incubation period was similar to those reported previously [12,27,28]. Mean and variance of the incubation period were estimated as 1.43 days and 0.48 days^2, respectively. The generation time in the figure includes the original datasets on different types of influenza virus (weighed by each sample size). The mean, median (25–75th percentile) and variance of the generation time were 2.92 days, 2.27 (1.41–3.67) days and 5.57 days^2, respectively.

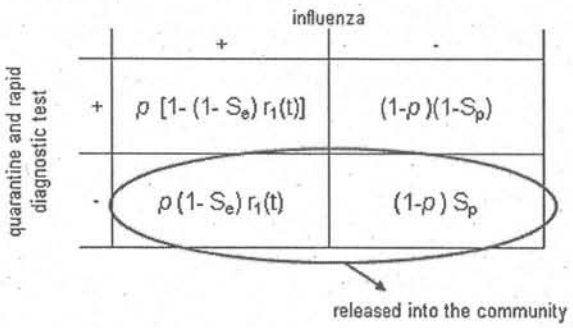

Figure 1
Performance of quarantine combined with rapid diagnostic testing. $r_1(t)$ is the probability of releasing infectious individuals following the quarantine of length t days. S_e = sensitivity of the rapid diagnostic test; S_p = specificity of the rapid diagnostic test; p = prevalence at the source community. Among infected individuals, those testing negative after quarantine of length t (i.e., $p(1-S_e)r_1(t)$) are released into the community. Among uninfected individuals, those testing negative (i.e., $(1-p)S_p$) are released.

Effectiveness of quarantine

Figure 3 shows the estimated effectiveness of quarantine as a function of time since infection (i.e., time since arrival). A different effectiveness measure (i.e., relative reduction of the risk of releasing "symptomatic infected" individuals regardless of infectiousness) is shown (dashed line) comparatively with the other two results showing the relative reduction of the risk of releasing "infectious" individuals in the presence and absence of the use of rapid diagnostic testing (thin and thick solid lines, respectively). It should be noted that the reduction of symptomatic infected individuals is based only on the incubation period, measuring a different concept of effectiveness from other two. The incubation period alone suggests that 95% effectiveness in preventing the release of symptomatic infected individuals is achieved by quarantine of 2.73 days.

We predict that 95% and 99% effectiveness in preventing the release of infectious individuals is achieved with quarantine periods of longer than 4.74 and 8.62 days, respectively. As can be observed from Figure 3, the impact of

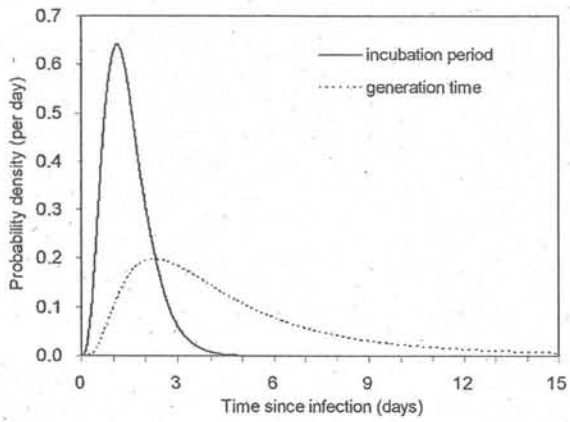

Figure 2
Probability density functions of the incubation period and generation time of influenza. Gamma distribution was employed to model the incubation period (i.e., the time from infection to onset), whereas lognormal distribution was fitted to the generation time (i.e., the time from infection of a primary case to infection of a secondary case by the primary case). The mean and variance of the incubation period and generation time are estimated as 1.43 days and 0.48 days^2 and 2.92 days and 5.57 days^2, respectively. For the original data see: [22] and [26].

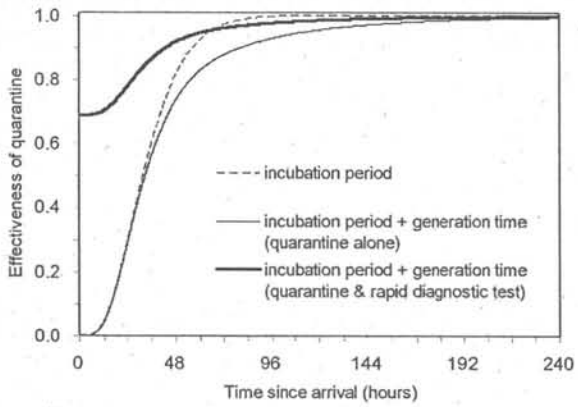

Figure 3
Effectiveness of quarantine with and without use of rapid diagnostic testing as a function of time since infection (i.e., time since arrival). Different effectiveness measures of quarantine are comparatively shown. The dashed line represents the effectiveness of quarantine, measured as the relative reduction of the risk of releasing "symptomatic infected" individuals (regardless of infectiousness) based on the incubation period alone. The two continuous lines measure the effectiveness as the relative reduction of the risk of releasing "infectious individuals" into the community, based on the incubation period, generation time and probability of symptomatic disease, with (thin) and without (thick) use of rapid diagnostic testing. The sensitivity of the rapid diagnostic test was assumed to be 69.0% (based on current test performance for seasonal influenza A [34]).

using rapid diagnostic testing on effectiveness is larger for a short quarantine period. If a rapid diagnostic test was available and this performed to the current standard for detecting influenza A in the pre-pandemic setting, we estimated that this additional testing would result in quarantine periods for longer than 2.59 and 5.71 days having effectiveness of over 95% and 99% respectively (Figure 3).

Sensitivity analysis

Given the above mentioned results, we investigated the sensitivity of quarantine effectiveness to four different lengths of quarantine (2.8, 4.8, 5.7 and 8.7 days) and to three different prevalence levels at the source (1%, 5% and 10%). The shortest length, 2.8 days, was suggested by the incubation period as being 95% effective in preventing the release of symptomatic infected individuals into the community. Two of the others (4.8 and 8.7 days) corresponded to 95% and 99% effectiveness in preventing release of infectious individuals by means of quarantine alone, and 5.7 days corresponded to 99% effectiveness when quarantine was combined with rapid diagnostic testing.

Figure 4 shows the median (and 5–95th percentile) numbers of infectious individuals who are released into the community after quarantine of specified lengths. The quarantine for 2.8 days could miss as many as 11 (5–16), 56 (45–68) and 114 (92–129) infectious cases for the prevalence of 1%, 5% and 10%, respectively in the 8000 arriving travellers considered. However, these misses were reduced to 4 (1–7), 20 (13–27) and 39 (28–53) cases by the quarantine of length 4.8 days, to 3 (0–5), 13 (7–19) and 27 (16–36) by 5.7 days and, moreover, to 1 (0–2), 4 (1–8) and 8 (4–13) cases by 8.7 days. The additional diagnostic testing could greatly reduce the released number of infectious individuals (Figure 4B). For the quarantine lengths of 2.8 and 5.7 days with rapid diagnostic testing, 3 (1–7), 18 (10–25) and 34 (25–45) cases and 1 (0–2), 4 (1–8) and 8 (4–14) cases, respectively, were expected be released into the community for the prevalence of 1%, 5% and 10%. All values for the quarantine period of 5.7 days combined with use of a diagnostic test were less than 3% of the total number of incoming infected individuals.

Figure 5 describes the ripple benefit of quarantine, expressed as the number of secondary transmissions caused by released infectious individuals. The qualitative patterns found were similar to those of Figure 4, but it should be noted that no secondary transmission was observed in the community in several scenarios. Quarantine of length 2.8 days, with or without rapid diagnostic testing, would lead to many secondary transmissions caused by released infectious individuals. When there was quarantine of 4.8 days without rapid diagnostic testing, we found 0 (0–2), 3 (1–7) and 5 (1–11) secondary transmissions. Extending quarantine to 8.7 days resulted in no secondary transmissions at prevalence levels of 1%, 5% and 10% (i.e., all were 0 except for 1 secondary transmission at the 95th percentile for all three prevalence levels). When diagnostic testing was combined with the quarantine period for 5.7 days, 0 (0–1), 0 (0–1) and 0 (0–2) secondary transmissions resulted. That is, even though quarantine alone for 8.7 days and quarantine combined with diagnostic testing for 5.7 days permit the release of several infectious individuals (up to 3% of the total number of incoming infected passengers), the majority of the released cases are at the late stage of infection and hardly cause secondary transmissions in the island nation (i.e. even in the worst case, only a few secondary transmissions would be expected).

Preventive performance of quarantine with rapid diagnostic testing

Figure 6 shows contour plots of PPV and NPV of quarantine combined with rapid diagnostic testing as functions of the length of quarantine and prevalence of influenza at the source. Given a fixed prevalence, PPV was greater for shorter length of quarantine (especially, for $t < 1$ day) due mainly to the relative increase in detection of true positives by rapid diagnostic testing (see equation (6)). However, it became less sensitive to the length of quarantine as the length became longer (for $t > 2$ days) and depended

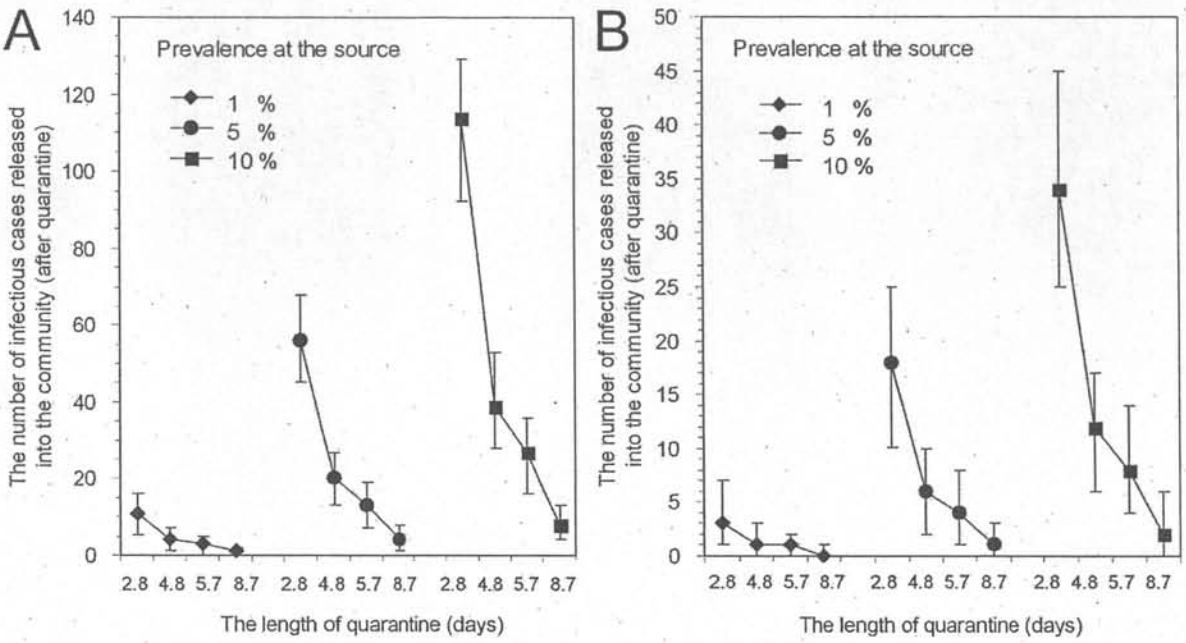

Figure 4

Sensitivity of the number of infectious cases released into the community (after quarantine) to the different lengths of quarantine and prevalence levels at the source. A. Quarantine alone. **B.** Quarantine combined with rapid diagnostic testing. Sensitivity of the number of released infectious cases into the community (after quarantine) is examined for different lengths of quarantine (2.8, 4.8, 5.7 and 8.7 days) and prevalence levels at the source (1%, 5% and 10%). Each dot represents median estimate of 100 simulation runs. The whiskers extend out to 5th and 95th percentiles of the simulations.

almost only on the prevalence (Figure 6A). Figure 6B demonstrates that NPV was on the whole very high and sensitive to both the length of quarantine and prevalence at the source. For prevalence levels up to 10%, NPV with quarantine for longer than 2 days could be greater than 99.0%. In particular, at a quarantine length of 6 days, NPV was greater than 99.9% for prevalence levels up to 10%. In other words, within the range of interest for quarantine lengths, PPV was mainly determined by the prevalence level (i.e., longer quarantine with rapid diagnostic testing does not load too many additional false positives on isolation facilities compared with the use of shorter quarantine and testing). Also, NPV can be extremely high, indicating that the release policy can efficiently suggest that the released individuals are likely to be true negatives.

Discussion

The present study provides theoretical support for border quarantine as a worthwhile pandemic influenza control measure for small island nations. Detailed advance planning for quarantine measures may therefore be justified during the pre-pandemic period. From our quantitative findings, we recommend a quarantine period of 9 days (rounding 8.7 days to the next integer) to reduce by more than 99% the risk of introducing infectious individuals and to ensure the absence of secondary transmissions caused by released infectious individuals in the community. If the use of rapid diagnostic testing can be combined with quarantine, the quarantine period could be shortened to 6 days (rounding 5.7 days to the next integer). To the best of our knowledge, the present study is the first to explicitly suggest an optimal length of quarantine for pandemic influenza derived from detailed epidemiologic characteristics of this infection. Although our recommendations are based on arbitrarily considering the specific percentiles of effectiveness, and although the absence of secondary transmissions depends also on the absolute number of incoming individuals, we believe that our findings (with realistic ranges of prevalence and the number of travellers) provide evidence-based estimates that can be used for pandemic planning. Quarantine might ultimately be unsuccessful in preventing importation of infected individuals [35]. However, delayed entry of the pandemic virus could provide time to introduce other social distancing and pharmaceutical interventions that may reduce the overall impact of a pandemic [1,9,30,36-39].

In recent studies, the optimal length of quarantine was considered by using the incubation period distribution alone, identifying the 95th or 99th percentile point of the

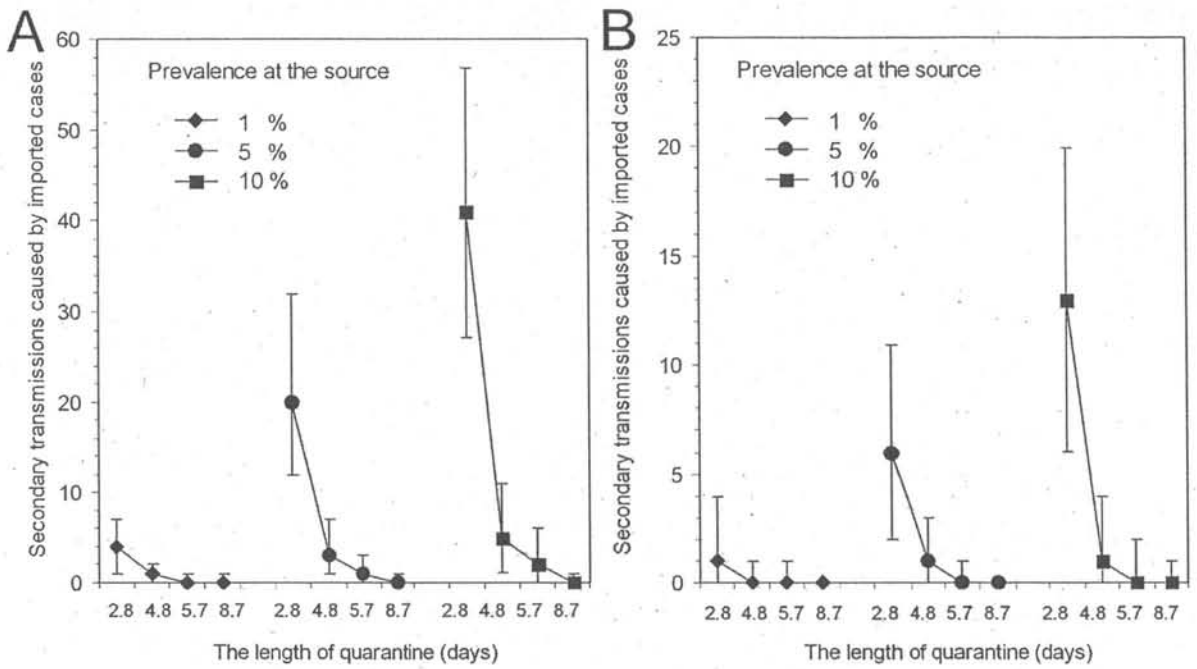

Figure 5

Sensitivity of the number of secondary transmissions caused by released infectious individuals to the different lengths of quarantine and prevalence levels at the source. A. Quarantine alone. **B.** Quarantine combined with rapid diagnostic testing. Sensitivity of the number of secondary transmissions caused by released infectious individuals is examined for different lengths of quarantine (2.8, 4.8, 5.7 and 8.7 days) and prevalence levels at the source (1%, 5% and 10%). Each dot represents median estimate of 100 simulation runs. The whiskers extend out to 5th and 95th percentiles of the simulations.

theoretical distribution [16-21]. For instance, 95th percentiles of the incubation period for severe acute respiratory syndrome (SARS) and smallpox were suggested to be 11–13 days [19,21] and 16–17 days [16] since exposure, respectively. Direct application of this concept to pandemic influenza suggests that the optimal quarantine period for pandemic influenza is only 2.73 days since exposure, which is far shorter than those for SARS and smallpox. However, since influenza involves a non-negligible fraction of asymptomatic infections [12,22], we also undertook the additional step of incorporating this feature into our assessment of quarantine effectiveness. This refinement permitted further elaboration of effectiveness estimates, which we believe contributes to theoretical considerations around the control of other infectious diseases. In addition, we reasonably showed the preventive performance of quarantine, expressed as the number of released infectious individuals and the ripple benefit expressed as number of secondary transmissions caused by them. Using further information on the contact structure in the island nation, our framework could be further extended to estimate the probability of extinction and the delay effect of epidemic spread imposed by quarantine, the latter of which was discussed by a recent study [35]. Although the recent study theoretically emphasises the difficulty of effective border control (including quarantine) [35], we stress that the epidemiologic characteristics of influenza (e.g., short incubation period and generation time) permit anticipating large ripple benefits from quarantine (given that importation may continue for only a short period of time before full border closure occurs).

Access to a highly sensitive test for pandemic influenza infection may increase the effectiveness of quarantine and shorten the quarantine period routinely required for incoming travellers. Preventive performance in finding true positives (i.e., PPV of quarantine combined with rapid diagnostic testing) appeared not to be very sensitive to the length of quarantine (for $t > 2$ days). This result suggests that if diagnostic test kit supplies are plentiful, then testing should be done early in quarantine. But if a test kit sparing approach is used (i.e., avoiding testing of those who become symptomatic) then there is not much benefit in delaying testing until after day 2 in quarantine. A test with both high sensitivity and high specificity would also allow for better use of resources if the travellers who tested negative are released into the community. Since PPV is mainly determined by prevalence at the source, it should be noted that an exit screening process at the source lowers the prevalence as well as PPV. Nevertheless, the effectiveness of

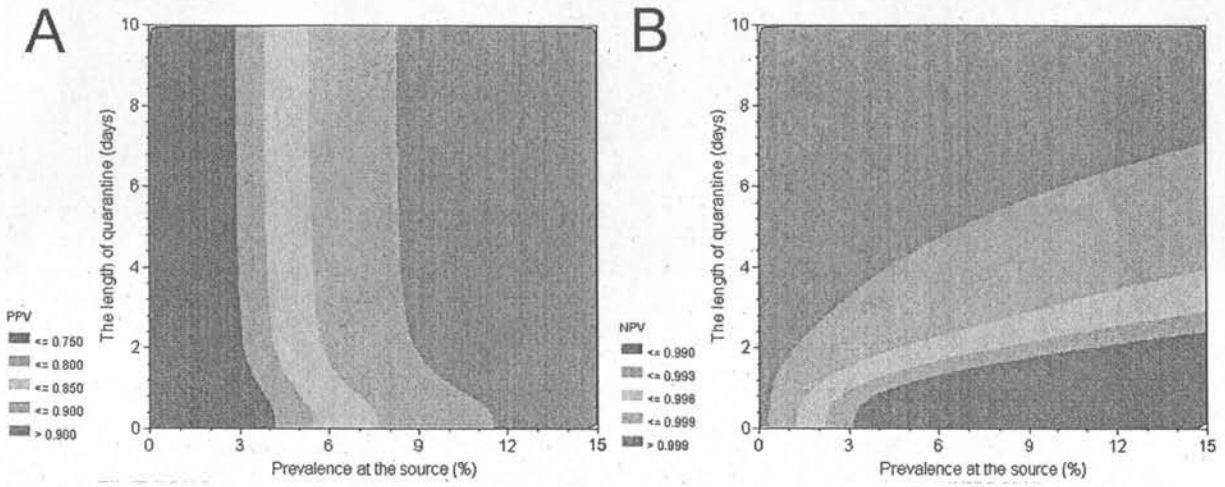

Figure 6
Diagnostic performance of quarantine with use of rapid diagnostic testing. A. Positive predictive values (PPV) and **B.** Negative predictive values (NPV) of quarantine combined with rapid diagnostic testing as functions of the length of quarantine and prevalence at the source. For the quarantine of 3 days or longer, PPV is less sensitive to the length of quarantine and depends almost only on the prevalence. NPV is sensitive to both the length of quarantine and prevalence at the source, achieving extremely high estimates to correctly release true negative individuals into the community.

quarantine itself is independent of the prevalence, and moreover, lower prevalence among incoming individuals yields a higher chance of extinction (or greater ripple effect of quarantine (Figures 4 and 5)). NPV of quarantine combined with diagnostic testing would be extremely high with quarantine periods for lengths of 3 days or longer, supporting our suggestion to release quarantined individuals testing negative to the rapid diagnostic test into the community (if there was high confidence in test performance parameters for the emergent pandemic strain). In light of our findings, island countries may consider including influenza testing capacity and test kit stockpiles in their pandemic plans. The use of rapid diagnostic tests, if available through stockpiling in advance or rapid delivery after pandemic emergence, may permit more effective border control, with more efficient use of isolation facilities and shortening of the quarantine period.

The operation of quarantine would be most feasible for islands with low traveller numbers and with pre-existing facilities that could be used for quarantine (e.g., hotels). Our study was indeed motivated by the consideration of protecting small island nations (e.g., in the South Pacific and Caribbean), because use of border control at usually just one or two international airports would be the major way in which the introduction of pandemic influenza could be prevented in these islands. Yet the analysis could potentially hold for larger island nations such as Australia, whose pandemic plan also includes border quarantine [40]. The logistics of quarantine might be far more demanding in Australia with its multiple international airports, but which nonetheless used strict maritime quarantine to successfully delay the entry of the 1918 pandemic [41]. Evidence about the geographic spread of influenza highlights the importance of quarantine in multiple locations [42-44]. Small countries with land borders and limited entry points could also use these approaches to delay entry of pandemic influenza as occurred for Israel in the 1957 influenza pandemic [5]. Facility-based quarantine could also be supplemented with ongoing surveillance in the community of those released from quarantine.

Our analysis employed a number of simplifying assumptions, among which we should emphasise the most important one. The detailed natural history parameters for seasonal influenza are not well documented and, moreover, we of course do not know if the incubation period and generation time of an emergent pandemic strain would be close to those of seasonal influenza documented in the limited number of publications to date. It should be noted that our analysis is solely based on the available published evidence and that the effectiveness of quarantine would be overestimated if the emergent strain of pandemic influenza had a longer incubation period or a longer generation time than we have assumed. However, the incubation period for human infection with H5N1 appears to be similar to other sub-types infecting humans [45]. This issue applies not only to the incubation period but also to other parameters, the role of which for each can be inspected using equations (4) and (5). For example, a historical analysis suggests that only 9% of infections resulted in an asymptomatic infection [46], which

would contribute to improved quarantine effectiveness (compared to our results). Given that our exercise indicates the critical importance of the incubation period and generation time, epidemiological investigations should be performed to better quantify these parameters and further inform evidence-based pandemic planning.

Extrinsic factors should also be more precisely quantified in future. As an indirect extrinsic effect, when infected individuals are released into the community and become infectious to others, recently quarantined individuals may be detected and isolated earlier than those who have not been quarantined [47]. Another issue of detection is that some island states may have access to laboratory-based PCR influenza tests which are far more sensitive and specific than rapid tests [48], which could offer the test results in a few hours and greatly shorten the length of quarantine.

To more appropriately quantify the effectiveness of quarantine, two other technical issues have to be discussed. The first is concerned with skewness of the offspring distribution (i.e. the distribution of the number of secondary transmissions caused by a single primary case). Although our study reasonably showed the absence of secondary transmissions for quarantine of certain lengths, we ignored the skewness (i.e., the presence of potential super-spreaders [49]), and thus, the uncertainty bounds might have been smaller than in reality. Although the mean and median of the predicted number of secondary transmissions are still valid, and even though the skewed offspring distribution was partly incorporated in the model with the right-skewed generation time distribution, super-spreading events played a key role in triggering the international spread during the epidemic of SARS, and in light of this, quantification of the dispersion parameter (of the offspring distribution) is needed in future studies. Another issue is related to our conservative assumption that all incoming individuals experienced infection upon arrival. Since it is impractical to know the time of infection for all incoming infected individuals (which should ideally be known when the quarantine is started at time $t = 0$), we adopted a worst case scenario where all infected individuals experience infection at $t = 0$ (see Appendix). This assumption could have overestimated the optimal length of quarantine. If further research demonstrates that influenza transmission on board flights is very rare, then it would be possible to set the quarantine period to begin at the start of the flight and therefore reduce its duration correspondingly following arrival. However, then we have to take into account the possible secondary transmissions during the quarantine period. Estimation of the effectiveness of imperfect quarantine (i.e., quarantine which allows secondary transmissions within the quarantine facility) would be far more complicated than our simpler model, and clarification on this point is a task for future research.

In addition to the present study, it should be noted that quarantine may be combined with reduction of travel volumes (e.g., even mandatory restrictions on non-essential travel) which would have a large effect if it occurred rapidly [35,50,51]. Substantial reductions of travel volumes could make the logistics of quarantine far more feasible for island nations and increase the probability of ensuring the absence of secondary transmissions (given the same prevalence level to that of a larger travel volume). Moreover, there is the potential usefulness of antiviral prophylaxis during the quarantine period which could theoretically reduce the number of infectious individuals. Despite the plausible reduction of infectiousness under antiviral prophylaxis, the probability of symptomatic infection will also likely be reduced, and thus, the detection of cases might be reduced. Unless the efficacy of antiviral prophylaxis and detection under this measure are well documented and promisingly high, it is difficult to determine if this countermeasure is likely to offer an overall positive impact on the success of quarantine, and this point should be clarified in future research. Another topic area to be clarified further is concerned with cost-effectiveness. Although we implicitly assumed that the governments of island nations may be willing to allocate quarantine facilities and spend sufficient money for diagnostic testing, these measures are economically demanding, especially for developing island nations. Extension of our method would permit estimating the required cost to achieve a specific ripple benefit (e.g., zero secondary cases for a certain period of time). Use of home-based quarantine (with health agency surveillance and support) is another cost-saving option that could be considered for islands with limited capacity for using facility-based quarantine (e.g., those with few hotels that could be requisitioned), but it should be noted that home-based quarantine might violate our assumption of ignoring secondary transmissions during the quarantine period. In practice, there may also be scenarios where it is not practical to separate all incoming travellers into separate quarters within a quarantine facility (e.g. parents with small children). In such cases, health workers may need to monitor such individuals especially closely and isolation may need to include a parent and infant when only one is symptomatic (all of which would increase costs).

Despite our simplifying assumptions, the present study reasonably suggests that use of quarantine has the potential to substantially reduce the risk of pandemic influenza arriving or at least significantly delay arrival, in small island nations. To ensure the absence of secondary transmissions for plausible ranges of prevalence at the source and a modest number of incoming travellers, we recommend quarantining the incoming individuals for 9 days if quarantine alone is implemented and 6 days if quarantine is combined with rapid diagnostic testing.

Conclusion

To inform border control for pandemic influenza in small island nations we examined the potential effectiveness of quarantine using several parameters which describe the epidemiologic characteristics of influenza. In particular, our modelling approach accounted for asymptomatic infection which is deemed a key requirement for successful influenza control [52,53]. The effectiveness was modelled as a relative reduction of the risk of introducing infectious individuals into the community as a function of time since arrival. We recommend a quarantine period of 9 days to reduce by more than 99% the risk of introducing infectious individuals and to ensure the absence of secondary transmissions. When rapid diagnostic testing is combined with quarantine, we recommend quarantine for 6 days to similarly prevent secondary transmissions.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NW and MGB conceived of the study and participated in its design and coordination. HN developed methodological ideas and performed statistical analyses. HN and NW did most of the work on drafting the manuscript. All authors read and approved the final manuscript.

Appendix

Earlier infection before quarantine

For simplicity, we consider the impact of earlier exposure to infection on the effectiveness of quarantine in terms of the frequency of onset during the quarantine period, which is relevant to the determination of the incubation period conducted by Anderson Grey McKendrick [15,29]. Let the length of quarantine be t. To account for earlier infections before starting quarantine at $t = 0$, we consider infection-age (i.e. the time since infection) for infected individuals, denoted by τ. Let $i(t, \tau)$ and $j(\tau)$, respectively, be the number of incubating infected individuals at quarantine period t and infection-age τ and the number of incubating infected individuals at infection-age τ at the beginning of quarantine $t = 0$ (i.e. $i(0, \tau) = j(\tau)$). $i(t, \tau)$ is written as

$$i(t,\tau) = j(\tau - t)\frac{\Gamma(\tau)}{\Gamma(\tau - t)} \quad \text{(A1)}$$

for $\tau - t > 0$ where $\Gamma(\tau)$ informs the survivorship function of incubating individuals at infection-age τ, i.e.,

$$\Gamma(\tau) = \exp\left(-\int_0^\tau \gamma(\sigma)d\sigma\right) \quad \text{(A2)}$$

where $\gamma(\tau)$ is the rate (or force) of onset at infection-age τ. Consequently, the density function of the incubation period, $f(\tau)$, is given by

$$f(\tau) = \gamma(\tau)\Gamma(\tau) \quad \text{(A3)}$$

Since we assume that there is no secondary transmission during quarantine period, $i(t, \tau) = 0$ for $t - \tau > 0$. The number of new symptomatic cases at quarantine of length t, $n(t)$, is

$$n(t) = \int_t^\infty \gamma(\tau) i(t,\tau)d\tau \quad \text{(A4)}$$

Replacing the right-hand side of (A4) by that of (A1), we get

$$n(t) = \int_t^\infty \gamma(\tau) j(\tau - t)\frac{\Gamma(\tau)}{\Gamma(\tau - t)}d\tau = \int_0^\infty f(t+\sigma)\frac{j(\sigma)}{\Gamma(\sigma)}d\sigma \quad \text{(A5)}$$

In our setting, all quarantined individuals have not experienced symptom onset before quarantine starts at $t = 0$. Assuming that all infected individuals eventually experience symptom onset (just for now), the total number of infected individuals satisfies

$$\int_0^\infty n(t)dt = \int_0^\infty j(\tau)d\tau \quad \text{(A6)}$$

Using (A5) and (A6), the density of symptom onset at quarantine period t (i.e. the frequency of symptom onset relative to the quarantine period t), $h(t)$, is

$$h(t) = \frac{n(t)}{\int_0^\infty n(t)dt} = \int_0^\infty \frac{f(t+\sigma)}{\Gamma(\sigma)}\frac{j(\sigma)}{\int_0^\infty j(s)ds}d\sigma \quad \text{(A7)}$$

Equation (A7) indicates the critical importance in understanding the earlier exposure in order to determine the optimal length of quarantine. That is, the density of symptom onset $h(t)$ always depends on the infection-age distribution (which is informed by $j(\tau)$) at the starting time point of quarantine ($t = 0$).

If the epidemic at the source country becomes endemic and reaches a stationary state with constant incidence Q, and if the infected travellers result from random sampling of infected individuals at the source country, we have $j(\tau) = Q\Gamma(\tau)$, leading to

$$h(t) = \frac{\Gamma(t)}{\int_0^\infty \Gamma(\tau)d\tau} \quad \text{(A8)}$$

which is equivalent to the survivorship of the incubating infected individuals (written as $1\text{-}F(t)$ in the main text using the cumulative distribution function of the incubation period $F(t)$). The simplification in (A8) holds only when a stationary state is the case at the source country, which is not likely to be observed in the event of an influenza pandemic.

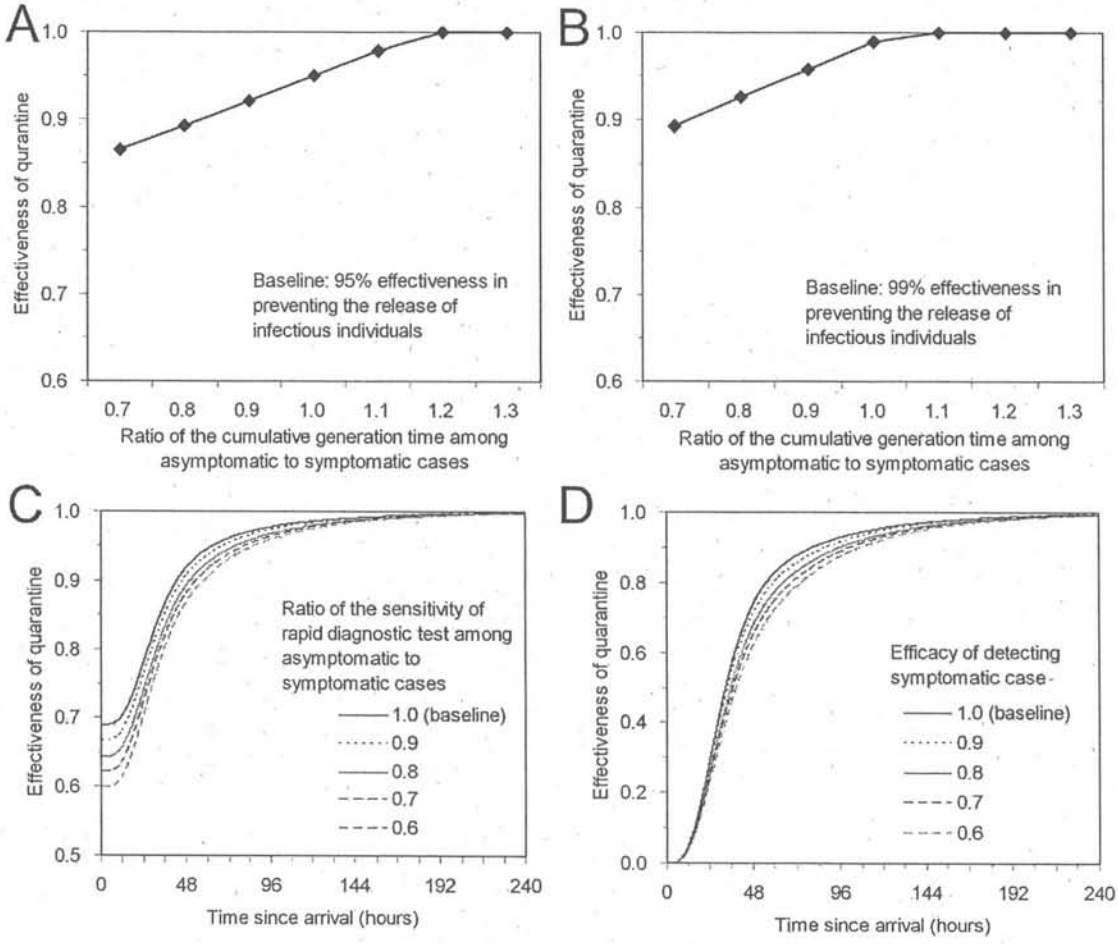

Figure 7

Sensitivity of the effectiveness of quarantine to uncertain epidemiologic variables. A & B. Effectiveness of quarantine as a function of the ratio of the cumulative generation time among asymptomatic to symptomatic cases. Sensitivity of the point estimates of the effectiveness with baseline values of 95% and 99% are examined in A and B, respectively. C. Sensitivity of the effectiveness of quarantine in the presence of rapid diagnostic testing to the diagnostic sensitivity among asymptomatic infected individuals. D. Effectiveness of quarantine with imperfect efficacy of case detection of symptomatic cases.

Thus, we need to use (A7) with some prior information of $j(\tau)$. Nevertheless, since the infection event is unobservable, we seldom know $j(\tau)$. Therefore, we recommend assuming that the start of quarantine $t = 0$ as the time of infection, which is the worst case scenario. Although the above mentioned arguments apply to symptomatic cases alone, we find exactly the same issue in the survivorship of infectiousness.

Differing parameters between symptomatic and asymptomatic cases

First, we consider the impact of differing generation times between symptomatic and asymptomatic cases on the effectiveness of quarantine. Although the generation time distribution of asymptomatic influenza infection has yet to be clarified, we at least theoretically separate the cumulative distributions $G_s(t)$ and $G_a(t)$, respectively, for symptomatic and asymptomatic cases. The equation (4) in the main text is replaced by

$$\varepsilon(t) = 1 - [\alpha(1 - F(t))(1 - G_s(t)) + (1 - \alpha)(1 - G_a(t))] \quad \text{(A9)}$$

Since $G_a(t)$ is unknown, we examine the sensitivity of $\varepsilon(t_\beta)$, where the effectiveness is calculated as $100\beta\%$ (i.e. $\beta = 0.95$ and 0.99), to different ratios of $G_a(t_\beta)$ to $G_s(t_\beta)$. Let c be $G_a(t_\beta)/G_s(t_\beta)$. $G_s(t)$ is assumed to be equivalent to $G(t)$ in the main text.

Figures 7A and 7B show the sensitivity of $\varepsilon(t_\beta)$ to different values of the ratio c with $t_\beta = 4.74$ and 8.62 days. When c

is smaller than 1 (i.e. when there are more asymptomatic infected individuals with extremely long generation times compared to symptomatic cases), the effectiveness measure (A9) becomes smaller than the baseline which we get from (4) in the main text. On the contrary, if the generation time of asymptomatic infected individuals is shorter than that of symptomatic infected individuals, the effectiveness rises up close to 100% with the assumed lengths of quarantine, suggesting the need to accumulate epidemiological evidence of the generation time.

Second, we investigate the impact of differing sensitivity of rapid diagnostic testing between symptomatic and asymptomatic cases on the effectiveness of quarantine. We theoretically separate the sensitivity S_e into $S_{e,s}$ and $S_{e,a}$ for symptomatic and asymptomatic cases, respectively. Since asymptomatic cases may shed lower titres of virus, we suspect that the ratio $S_{e,a}$ to $S_{e,s}$ ($r := S_{e,a}/S_{e,s}$) is smaller than 1. The equation (5) in the main text is replaced by

$$\varepsilon_d(t) = 1 - [(1 - S_{e,s})\,\alpha(1 - F(t))(1 - G(t)) + (1 - S_{e,a})\,(1 - \alpha)(1 - G(t))] \quad \text{(A10)}$$

Figure 7C shows the sensitivity of $\varepsilon_d(t)$ to different values of the ratio r assuming that $S_{e,s} = 0.69$. As the ratio r becomes smaller (i.e. as the diagnosis of asymptomatic infected individuals becomes more difficult than that of symptomatic cases), the effectiveness also becomes smaller. Although the difference in $\varepsilon_d(t)$ is greater for short quarantine periods, the effectiveness becomes less sensitive to r as the length of quarantine becomes longer. We estimated that 99.0% effectiveness in reducing the risk of introducing infectious individuals into the community is achieved with $t = 5.71$ days using the rapid diagnostic test of $r = 1.0$ in the main text. The effectiveness estimate with the same length of quarantine and $r = 0.6$ is still as large as 98.1%.

Imperfect case detection

Although we considered perfect detection of symptomatic cases upon symptom onset during quarantine in the main text, here we examine the sensitivity of the effectiveness of quarantine to differing efficacy of case detection. Let the efficacy of case finding be k which we assumed as 1 in the main text. In reality, it might be difficult to detect all flu-like symptoms (i.e. $k < 1$). The equation (4) in the main text is replaced by

$$\varepsilon(t) = 1 - [\alpha(1 - kF(t))\,(1 - G(t)) + (1 - \alpha)\,(1 - G(t))] \quad \text{(A11)}$$

It should be noted that k influences symptomatic cases alone, because the detection of symptoms does not apply to asymptomatic infected individuals. Figure 7D shows the sensitivity of $\varepsilon(t)$ to different values of the ratio k which was assumed to lie in the range of 0.6 – 1.0. As the ratio k becomes smaller (i.e. as the detection becomes less efficient), the effectiveness becomes smaller. The difference in $\varepsilon(t)$ between different ratios k is particularly highlighted when the quarantine period is between 2 and 5 days. Nevertheless, for the shorter and longer quarantine periods, difference in $\varepsilon(t)$ is almost negligible. In the main text, we estimated that quarantine for 8.62 days achieves 99.0% effectiveness of reducing the risk of releasing infectious individuals into the community with $k = 1.0$. The effectiveness estimate with the same length of quarantine and $k = 0.6$ is still as large as 98.2%.

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平成21年度 厚生労働科学研究費補助金 厚生労働科学特別研究事業「新型インフルエンザ（インフルエンザA/H1N1swl(注)）発生への検査、調査についての準備及び初期対応の総括と病原体検査や感染者調査に関する今後の国と地方との連携強化及び対応能力強化に関する緊急研究」について

（注）新型インフルエンザの標記について

2009年にpandemicを引き起こした新型インフルエンザA/H1N1ウイルスは、ブタに常在するA/H1N1sw(swine)ウイルスから由来したことから、発生当初は季節性インフルエンザA/H1N1ウイルス（A/ソ連型）と区別するために、influenza A（H1N1）swine-lineage（A/H1N1swl）という表記法が暫定的に用いられた。このため、その時点で研究を開始した本研究課題名は「インフルエンザA/H1N1swl」としているが、その後、新型ウイルスの正式名はpandemic（H1N1）2009また短縮表記法としてA/H1N1pdm（pdmはpandemicの略）を採用することになっている。疾患名についても、これまでいくつかの標記が使用されてきた経緯があり、本報告書でも「（H1N1）2009パンデミック」「パンデミック（H1N1）2009」等の複数の標記方法を使用している。

＜報告書の概要＞

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【研究の趣旨】

平成21年4月に発生した今回の新型インフルエンザに対し、国立感染症研究所における対応を整理し記録した。また、国立感染症研究所が主たる役割を担っている病原体検査及び感染者調査について、今回の経験を今後の感染症危機管理対応に活かす観点から、地方衛生研究所、検疫所、国立保健医療科学院等の関係機関における対応も含めて検証及び検討を行った。検討対象とする対応の期間は、主として発生初期（概ね平成21年4月～7月）とし、これらの対応に関連する事前の準備等についても対象とした。

【 総括の概要 】

感染症コントロールの根本は、(i)事前の準備、(ii)流行の迅速な把握、解析、(iii)機敏な対応、(iv)流行ごとに新規に学んだことを生かして次に備えることである。インフルエンザに限らず、感染症の対応は、走りながら最善の対応をせねばならない側面もあるが、今回の新型インフルエンザに対する対応においては、当初、最悪の事態として想定していた高病原性鳥インフルエンザA/H5N1からの発生ではなかったものの、その準備として行ってきた国立感染症研究所における体制整備、病原体検査、疫学調査等にかかる国立感染症研究所一地方衛生研究所一検疫所の連携基盤が今回の円滑な対応において大いに役立った。

今回の初期対応については、従来からの国内外の連携を糧に概ね適切であったといえるが、原因となるウイルスの性質が季節性並の病原性にとどまっていたことが幸いだった面もある。今回の経験から、今後とも国内外の関係機関の連携の維持、強化、弛まぬ基礎研究の推進と国民の信頼に基づく感染症対策への強い国のポリシー確立を図る為の多くの教訓を得た。

【 分担研究の概要 】

I　国立感染症研究所における対応

1．国立感染症研究所における対応

（1）事業継続計画（ＢＣＰ）の作成　　[渡邉]

【要　旨】

国立感染症研究所では、政府全体における高病原性鳥インフルエンザA/H5N1からの新型インフルエンザの発生を想定し、平成21年4月までに検査等業務の事業継続計画を策定し、所内の応援体制、業務の優先度等について調整を行ってきていた。今回はこれを基盤としての対応体制が整備されていたので、迅速に対応することができた。

【報告の概要】

○　平成 20 年 1 月、副所長を中心に国立感染症研究所における事業継続計画の策定の検討を開始。①新型インフルエンザに関するウイルス検査、②新型インフルエンザに関する疫学調査、情報収集・解析、③（通常業務である）検定・検査、④健康管理、⑤総務部関係　の各業務について WG を設けて検討を行い、平成 21 年 3 月には「国立感染症研究所新型インフルエンザ対策行動計画」の策定をほぼ終了し、平成 21 年 4 月 27 日には本計画に基づく対応を開始した。

○　本計画では、特に上記①②に対する業務体制を強化するため、主として担当するインフルエンザウイルス研究センター、感染症情報センター以外の研究部、総務部

の職員も含めた全所的な応援体制を組むこととして所内の合意を事前に得ており、今回の対応においては円滑に機能した。

＜課　題＞

○　関係部、関係者間の意思疎通・情報共有を支える基盤的整備（情報マネージメントシステム等）が不十分であった。

※　現在、円滑な庁舎間の遠隔会議の実施方法等を含め、情報共有方法の等の改善を図りつつある。

（2）国内外の主要会議等への参画　　[岡部][田代]

【要　　旨】

国立感染症研究所インフルエンザウイルス研究センター及び感染症情報センターの両センター長をはじめ国立感染症研究所の職員は、今回の新型インフルエンザの発生以前より国内外の多くの新型インフルエンザ関連会議に専門家として参画した。発生後も国内外における対策決定への貢献、最新の情報の収集と共有を行った。これらが我が国の対応に必ずしも反映されなかった部分もあった。

【報告の概要】

○　以下の会議等への参画をとおして、国内対応及び国際対応に貢献するとともに、国際会議への参加を通じて得た最新の情報を厚生労働省等に還元することにより、国内対応に関する判断材料として活用された。

＜主な国内会議等＞

・　新型インフルエンザ対策専門家会議（厚生労働省）＜平成21年4月以前＞
・　新型インフルエンザ対策本部専門家諮問委員会（内閣官房）＜平成21年5月以降＞
・　健康危機管理調整会議（厚生労働省）
・　衆議院予算委員会
・　タミフル調査専門委員会（厚生労働省）
・　新型インフルエンザワクチン意見交換会（厚生労働省）　等

＜主な国際会議等＞

・　WHO国内インフルエンザセンター緊急対応計画に関する作業部会（ジュネーブ）
・　WHOインフルエンザPCR作業部会（ジュネーブ）
・　新型インフルエンザ準備に関する政府間会議（IGM）（ジュネーブ）
・　WHO総会（ジュネーブ）
・　ノイラミダーゼ阻害薬感受性ネットワーク（NISN）会議（ロンドン）
・　新型インフルエンザ再検討国際会議「パンデミック回避計画」（イタリア・シエナ）
・　WHO(WPRO/SEARO)国内インフルエンザセンター会議（北京）
・　新型インフルエンザ対応と準備に関する国際シンポジウム（北京）
・　米国ACIP会議（アメリカ）
・　H1N1ワクチンに関するWHO／SAGE会議（ジュネーブ）
・　WHO(WPRO/SEARO)会議（バンコク）
・　WPRO 各国緊急感染症対応部局及びIHRフォーカルポイント会議(マニラ）等

※　その他、WHO、GHSAG等が行った国際電話会議にも参画した。

＜課　題＞

○　限られた時間、マンパワーの中で国内対応と国際対応に同時に対応していたため、

さらに円滑かつ効率的な対応方法への改善が必要がある。

※　人員の効率的な活用のためのシステム的な改善も検討することが重要

○　国際的な対応の方針、状況については、適宜、厚生労働省等と共有していたが、水際対策から国内対策への重点の移行時期等に関しては、必ずしも我が国の対応において迅速に反映されなかった部分があった。

※　今後とも、専門家としての意見の適宜適切なとりまとめ及びこれらに関する対策立案関係者との意思疎通を更に図る必要がある。

2．インフルエンザウイルス研究センター(注)における対応

（注）インフルエンザウイルス研究センター

平成21年4月1日、それまでのウイルス三部の一部として実施していたインフルエンザ関連研究・業務を一元的に担当する目的でインフルエンザウイルス研究センターが発足した。

（1）WHOインフルエンザ協力センター等としての対応　［田代］

【要　　旨】

世界４カ所のWHOインフルエンザ協力センター及びワクチン品質管理担当ラボラトリーに指定されている機関の一つとして、今回の新型インフルエンザの発生前から状況の収集・分析とWHOにおける対応方針の検討等に貢献するとともに、世界各国の担当者との強い信頼関係が基盤となって、世界的健康危機に対応した国際貢献を果たした。

【報告の概要】

○　今回の新型インフルエンザの発生確認以前から米国CDC、WHO世界インフルエンザ監視ネットワーク（GISN）等よりブタ型インフルエンザウイルスH1N1によるヒト感染例の発生、メキシコ南部でのインフルエンザ様疾患の流行拡大等の情報が速やかに共有され、WHOインフルエンザ協力センターの一員として情報収集と解析にあたった。

○　WHOによるフェーズ４宣言以前より、当該ウイルスのウイルス学的解析に関する情報を共有し、その遺伝子配列から予想されるウイルスの性状を調べ、他の協力センターとともに新型A/H1N1pdmウイルスの遺伝子検出のためのPCRプライマーとプローブの設計を提案し、我が国においても設計・作成をいち早く開始した。

○　WHOにおけるフェーズ引き上げ、ウイルスの取扱いレベル、ワクチン開発とその効果等に関する検討に参加するとともに、厚生労働省、内閣官房等との情報共有を行った。

○　その他、世界各国とウイルス特性や対応等に関する情報を交換するとともに、アジア地域を中心とするウイルス診断検査等にかかる技術支援を行った。

○　国内における新型インフルエンザワクチンの製造株決定に関する会議を主導し、株の選定、推奨を行った。

＜課　題＞

○　インフルエンザウイルス研究センターは発足したばかりであったため、新規職員等の教育訓練等が十分に終了していない状況での対応であった。

※　今回の経験をもとに、ワクチンの品質管理を担うEssential Regulatory Laboratoryとしても世界の期待に添えるよう実力をつけていきたい。

○　多くの国では、WHOのパンデミック警戒レベル（フェーズ）に応じた対応計画が作られていたが、流行の地理的な拡大を規準としたことから多くの問題が生じた。

※　さらに適切な指標を設定していく必要がある。

○　世界における対応と我が国の対応が一致していない部分も見受けられたが、情報共有と対応の判断についてのプロセスにはさらなる改善が必要と考えられる。

※　多くの関係者との意思疎通の円滑化、大量の情報を適宜適切な者と共有する方法等に関するさらなる検討が必要

（2）国内のウイルス診断検査体制の構築　　[小田切]

【要　　旨】

今回の新型インフルエンザ発生以前に高病原性A/H5N1鳥インフルエンザを想定して検疫所、地方衛生研究所に対して準備を行っていたPCR法による診断検査系を新型A/H1N1pdmウイルス用に修正し、新型インフルエンザが本邦に上陸する前に全国規模での検査体制を構築し、地方衛生研究所と連携・協力により検査系の更新も行った。また、これらプライマー、プローブの情報等をWHOのPCRワーキンググループに提供する等により、海外の検査機関での診断検査系の開発に貢献した。

さらに、新型インフルエンザウイルスに対する抗インフルエンザ薬耐性株サーベイランス体制を地方衛生研究所と連携して構築した。

【報告の概要】

○　今回の新型インフルエンザ発生以前より、地方衛生研究所、検疫所に対して高病原性A/H5N1鳥インフルエンザを想定したウイルス検出検査系の構築の支援と検査技術訓練を実施しており、今回の対応の基盤となった。

○　米国CDCが公表したカルフォルニア株の遺伝子配列をもとに、WHOによるフェーズ4宣言以前からプライマー、プローブの設計を開始し、平成21年5月2日には全国の地方衛生研究所、検疫所等への配布、検査指針等の提供が終了し、全国規模での診断検査体制の構築が可能となった。

また、7月には、地方衛生研究所からの変異株の情報が速やかに提供され、プローブの再設計と再配布を行うことにより、検査精度の向上が図られた。

○　初期においては、新型インフルエンザへの感染疑い者の検体検査を地方衛生研究所、検疫所と並行して実施し、国立感染症研究所が確定診断を担当した。

○　地方衛生研究所との連携・協力により、実施方針、要綱、マニュアル等を作成、配布し、新型インフルエンザ抗インフルエンザ薬体制株サーベイランスの立ち上げ

と全国規模で実施体制を構築した。

○　インフルエンザウイルス研究センターにおいては、事前に作成していた国立感染症研究所の行動計画に基づいて他部署による応援体制を構築することにより、膨大な業務を比較的円滑に対応することができた。

＜課　題＞

○　当初、新型インフルエンザ発生時の検査については、「医療機関における診断のための検査ガイドライン（2009 年 5 月 1 日改定）」に基づいた作業方針が合意されていたが、その後、厚労省本省においてその方針変更がなされたことから、現場での混乱が生じた。

※　今後、現場の対応状況を反映した、現実的な対応策を検討することが必要である。

○　今後とも、国立感染症研究所と地方衛生研究所、検疫所とのさらなる連携、協力体制の維持と強化が必要と考えられた。

3．感染症情報センターにおける対応　［谷口］

【要　　旨】

今回の新型インフルエンザへの対応として感染症情報センターが行ったサーベイランス、疫学調査、コミュニケーションの３つの分野について、その内容とLesson learnedを記述し、今後の対応に向けての資料とする。今後は、国家としての健康危機管理のための明確な戦略をもってシステムを見直し、国と地域で一体となって構築する全体の体制が必要である。

【報告の概要】

本分担報告においては、分担研究者が実施した本研究課題に関連する他研究課題により得られた成果の一部も掲載した。

（1）サーベイランス

※　平成 21 年 4 月 29 日～7 月 24 日までに実施したものを中心に記載

○　①全数届出、②疑い症例調査支援システム、③状況のモニター、④重症例の把握、⑤病原体サーベイランス、⑥全体のパンデミックのインパクト（超過死亡）に関して情報の収集・解析をとおし、そのデータを対策実施の資料として厚生労働省に提供した。

○　研究的なサーベイランスとして、⑦メーリングリスト（ML）インフルエンザ流行前線情報データベース（ML-Flu-DB）、⑧学校欠席者サーベイランス、⑨薬局サーベイランスによる情報の収集・解析を行い、協力自治体、厚生労働省、文部科学省等と共有した。今回の経験により、これらの有用性について一定の評価ができたことから、今後は全国的なシステムとして活用することを検討すべきであると考えられた。

＜課　題＞

○　以前より、新型インフルエンザの発生を想定したサーベーランスの実施方法、改

善等の議論が行われていたが、今回の対応においては体系的に実施には間に合わなかった。このため、医療機関、自治体からの届出内容・方法がしばしば変更され、法制度に基づくサーベイランスの中心システムである NESID についても状況にあわせた柔軟な運用ができなかったことから、ファックスや緊急回避的な届出システムの追加等が行われ、情報収集・共有の体制が混乱した。

※ 今後、サーベイランス全体として検討を行ってシステムを設計すること、システムの運用の責任の所在を明確にして状況に即した柔軟な運用ができるようにすること等の検討を行い、より迅速で精度の高いサーベイランスを目指すことが必要である。

（2）積極的疫学調査の支援

○ ①成田空港検疫所（隔離、停留者）、②神戸市・兵庫県、③大阪府、④福岡市・福岡県、⑤船橋市、千葉県、⑥沖縄県、⑦宮古島市において感染者を中心とした積極的疫学調査の支援を行うとともに、その状況を厚生労働省と共有した。

○ FETP（実地疫学専門家養成コース）研修員がこれらの疫学調査に加わり、人員養成の面からも有用であった。

○ 実地疫学調査と並行して、①国立感染症研究所の血清銀行の保管血清を用いたパンデミック発生前の国民の抗体保有状況、②集団発生時の感染暴露状況を検討するため神戸市における医療従事者等の抗体保有状況、③既存の感染症流行予測調査事業を活用したパンデミック中の国民の抗体保有状況等の血清疫学的調査を実施し、その結果を厚生労働省と共有、公表した。

＜課　題＞

○ 関係者の努力により調査への支障はなかったが、緊急時に大規模な調査を実施するための予算的措置、体制等に関しては大きな課題を残した。

※ 今後、必要に応じて適宜適切な調査の実施を担保する予算、人員の措置、人材育成等を図る必要がある。

（3）国際サーベイランス、海外情報の収集

○ WHO、米国 CDC、ECDC、FDA、OIE に掲載される各国の患者・死亡者等の状況、各種サーベイランスの手法及び実施状況、各種ガイドライン等を中心に情報収集し、国内サーベイランスのデータと比較・分析する等により対策の基礎資料とした。

○ 米国CDCのMMDWをはじめとする各種論文や研究者のネットワークを通じて情報を収集し、関係者との共有を図るとともに、翻訳してホームページに掲載する等して国内の関係者、国民への積極的な情報提供・発信を行った。

○ これらの業務は、新型インフルエンザ発生以前に作成された国立感染症研究所の行動計画に基づいて関係者の応援体制を組むこととされていたことから、一部でこの仕組みを活用して作業を行った。

＜課　題＞

○ 応援者による作業も含めて、実施すべき作業の優先順位の決定、確認作業の段階での作業の停滞等、作業全体の効率的実施のための調整方法等に課題を残した。

※　これらの作業を支援する方針やシステム、翻訳・確認のスペシャリストの確保等も必要と考えられる。

（4）情報発信、コミュニケーション

○　情報発信は、主として①Web（ホームページ）、②メディア意見交換会・報道対応により行った。

○　①としては、海外情報の日本語を含む国内向け情報発信と日本国内の情報を英訳しての海外向けの提供を行い、アクセス数は平成21年5月末は約63万リード／日に至っている。平成21年4月28日～12月31日までに掲載した国内向け情報の原稿総数は369、海外向け情報は27であり、その他、症例報告数・死亡者数を図表として105回のアップデートを行った。

○　②については、以前よりマスコミ関係者に感染症に関する理解を深めてもらい、国民への正確な情報提供につながることを目的に定期的に実施していた。新型インフルエンザに関しては、平成21年4月27日を皮切りに4月中に2回、5月は10回、6月に4回と集中的に開催し、その後もほぼ月に2回のペースで開催している。これらの実施に際しては、全所的な支援が行われた。

○　国立感染症研究所内では、当初、感染症情報センター内でのミーティングは毎日、感染研全体としては感染症情報センターとインフルエンザウイルス研究センターの主体が戸山庁舎と村山庁舎に分かれていることも勘案し、定期的にテレビ会議を頻回に行って疫学情報、病原体情報、国際会議での情報等、技術的な情報共有と議論に基づく意志決定を行った。

＜課　題＞

○　今回のような危機管理時には多くの情報が行政ルートを含む様々なルートで公開されるが、メディアを通じて国全体に提供されるものも多く、公衆衛生従事者や臨床医等の専門家が必要とする情報が適宜適切に提供されていなかった可能性がある。

※　米国では、情報のネットワークがPHIN（Public Health Information Neuwork）として一元管理され、専門家への情報はHAN（Health Aleart Network）において個別に提供されている。今後、我が国においても情報の収集体制とリンクした提供体制が必要。

○　情報発信にかかる翻訳を含むの作業等については、人的、予算的の確保に大きな課題を残した。

※　危機管理時における国全体としての明確な戦略をもち、今後の対応に活かしていくことが必要。

4．検疫所との連携・協力による対応　［藤井］

【要　　旨】

今回の新型インフルエンザ対応において検疫所と国立感染症研究所が協働して行った病原体検査、隔離者等の疫学調査について、その準備状況、実際の対応について関

係者からの意見聴取も踏まえて記録・検証した。
今回、概ね円滑に協働した対応が行われたが、さらに組織的な連携・協力体制の強化を図る必要があると考えられた。

【報告の概要】

○ 病原体検査の速やかな体制整備については、以前より行われていた高病原性鳥インフルエンザH5N1からの発生を想定したPCR検査による診断検査系の準備が有用であった。

○ 成田空港検疫所における我が国で初めて確認された感染者に対して、国立感染症研究所の疫学専門家による調査を実施した。

○ その他、検疫業務への人的支援として、国立感染症研究所の職員を派遣した。

＜課　題＞

○ 全国規模で検疫所との協働が必要とされる事例についての、双方の役割分担の明確化と共有認識の醸成、日頃からのコミュニケーションの確保の不十分さがあった。

※ 持続的、組織的な連携・協力体制の強化を図るための検討も必要である。

Ⅱ　地方衛生研究所における対応　［田中］

札幌市、秋田県、東京都、富山県、愛知県、大阪府、奈良県、神戸市、山口県、沖縄県の地方衛生研究所が研究協力

【要　旨】

病原体検査を中心に、診断検査、ウイルスサーベイランス及びその実施体制について、研究協力者とともにレビューし、これらを踏まえて課題等を検討した。
今回のインフルエンザパンデミックでは、地方衛生研究所は、その診断検査、情報発信等についての対応能力を活かして役割を果たし、効果的かつ円滑な対応に貢献した。その一方で地方衛生研究所間の試験法、人材、体制等の格差があることも明らかとなったことから、今後、地方衛生研究所の役割と関係機関との連携システムの再構築、感染症対応における地方衛生研究所の役割についての法制化等による明確化も必要と考えられる。

【報告の概要】

（1）遺伝子診断検査による検査体制

○ これまで想定されている高病原性鳥インフルエンザウイルス A/H5N からの発生を想定した事前の対応準備（遺伝子診断検査に関する技術研修、情報提供・共有体制の構築等）は今回の新型インフルエンザ対応において大いに有用であった。

○ 国立感染症研究所からの遺伝子診断検査のための試薬等の提供（H21.5.2には、全国の地方衛生研究所で受け取り完了）及びそれまでの事前調整が迅速になされた。

○ 国立感染症研究所から提供されたプローブ（遺伝子診断検査用試薬の一つ）領域の遺伝子変異情報が地方衛生研究所から報告され、その情報に基づき早期かつ円滑なプローブの改良が行われ、診断精度が高まった。

○　地方衛生研究所感染症対策部会からの提言等により、厚生労働省が現実的かつ迅速な判断を行い、当初、WHO において BSL３とされた新型インフルエンザウイルスの取扱いレベルを BSL２とする旨の通達が発出された。

＜課　題＞

○　地方衛生研究所における人員の確保、機器整備状況の改善

※　地方衛生研究所における日常の種々の業務に加えて新型インフルエンザの大量の検査検体への対応とその両立、或いは業務の優先順位の判断が困難であった。今後、緊急時対応における人員確保、機器整備、業務の優先順位の明確化等において改善を要する地方衛生研究所が多いと考えられる。

○　地方衛生研究所の検査技術への評価、信頼性

※　初期における確定診断は、地方衛生研究所と国立感染症研究所とのダブルチェックにより行われたが、作業が混乱する要因となったとともに、検査技術の過小評価と受け止めた地方衛生研究所も多かった。

※　地方衛生研究所においても、平素からのクロスチェック等による精度管理や研修システムの構築・継続が必要である。

○　頻繁に行われた厚労省からの検査方針等の変更及びこれらへの対応

※　科学的知見と現場での対応状態の把握に基づく適宜適切な対応方針の決定方法については、さらに検討が必要と考えられる。

○　迅速診断簡易キットと遺伝子診断検査との結果の乖離への対応

※　今後とも得られたデータをもとに原因等の詳細な解明や対応について検討する予定。

（２）ウイルスサーベイランス

○　地方衛生研究所の機器整備等の状況を踏まえ、地方衛生研究所、国立感染症研究所が協力してオセルタミビル薬剤耐性株の検出系の評価を行った。

○　重症化症例について、病状進行に及ぼす影響等について詳細に解析を行った。

＜課　題＞

○　地方衛生研究所における人員の確保、機器の不足等への対応

※　地方衛生研究所における機器（シークエンサー、リアルタイム PCR 等）の整備状況等に差があり、発生後に整備されたところもある。

○　緊急対応時における諸経費等の確保

※　地方衛生研究所により予算・人員面での状況等に差があり、対応に難渋した地方衛生研究所もある。

（３）地方衛生研究所における体制

○　近畿地方においては、近隣自治体の地方衛生研究所との連携・協力を謳った健康危機対応の協定書による検査対応が行われた。

○　各自治体においては新型インフルエンザに対する事前準備が開始されていたことから、研修、模擬訓練等を含め、危機意識のモチベーションの高まりを背景にスム

ーズに対応できたところが少なくない。

○　地方感染症情報センターとしての情報発信等についても、その役割を果たすことができた。

＜課　題＞

○　各地方衛生研究所では、今回の経験をもとに運用指針の見直し等により実際的な対応体制を再検討することが必要である。

※　各地方衛生研究所では、人員の不足から職員の疲弊があったが、職員への負荷は必ずしも検体数の増加と相関せず、応援体制を含めた運用の方法に影響されると考えられた。

○　自治体により地方衛生研究所における対応の準備状況、検査能力、機器整備、人員確保、予算等、地方衛生研究所（間）－保健所－医療機関－本庁（県庁等）－国（厚生労働省等）との連携・連絡体制等の状況が異なり、改善を要する部分も多い。

※　全国の地方衛生研究所に対するアンケートを実施した結果、自治体により機器整備状況等に差があった。また、協力研究者からの報告では自治体によって関係機関との連携等の状況も異なっていた。今後は、地方衛生研究所と関係機関それぞれの役割と連携システムの再構築、地方衛生研究所の法制化等による各機関の役割をより明確にすることが不可欠と考えられる。

Ⅲ　国立保健医療科学院における人材育成　［林］

【要　旨】

新型インフルエンザについて国の実施した対策を総括し、感染症危機管理対策に係る人材育成のあり方、医療情報ネットワークの活用について検討を行った。

国の対策に関しては、水際対策、検査体制、リスク評価の面で改善の必要性が示唆された。地域に応じた対応を臨機応変に実施するには、検査機能と疫学機能の両面からの人材育成が必要と考えられた。

【報告の概要】

○　国の対策に関して、水際対策、検査体制、リスク評価の面で改善の必要性が示唆された。水際対策については、健康危機管理情報を収集し、迅速に病原体の特徴を把握する体制が必要であり、地域に応じた対応を臨機応変に実施するには、検査機能と疫学機能の両面からの人材育成が必要と考えられた。

○　国立保健医療科学院における研修は、新たに加わった「健康監視」を含めた保健所の対応に少なからず寄与していた。しかしながら、保健所は都道府県本庁で決定された方針に従ってどのように対応するかが求められていることから、今後は、健康危機管理対策を立案する都道府県本庁の職員を対象とした研修の必要性が示唆された。

○　感染症危機管理対策は、危機対応に当たる機関の効率的で持続的な連携が不可欠である。特に、限られた人員、予算、時間の制約下で柔軟に事案に対応するためには、国及び都道府県において情報政策を統括する責任者を設置し、情報システムを緊急に運用できる体制の構築が必要であり、健康危機管理情報の分析、評価の向上

に向けた研修の必要性が示唆された。

＜課　題＞

○　感染症法に基づく感染症発生動向調査の中核を担う地方衛生研究所については、能力の平準化が不可欠であり、このためには、検体分与、運搬等に係る制度の見直しが必要である。

○　本研究における検討を踏まえ、更なる科学院の健康危機管理分野に係る研修の充実・強化を図る必要がある。

パンデミック(H1N1)2009 Pandemic (H1N1)2009

IDSC 更新情報

神戸市および兵庫県における新型インフルエンザ集団発生疫学調査報告

第1部
全体像編

2009年8月31日

国立感染症研究所 実地疫学専門家養成コース(FETP)
国立感染症研究所 感染症情報センター

全文PDFファイル(972KB)
※ダウンロードはこちらから

第1部要約

新型インフルエンザの発生状況を把握し、臨床・疫学的特徴を明らかにし、感染拡大防止対策につなげるために、神戸市、兵庫県における新型インフルエンザ患者からの聞き取り調査や神戸市保健所等からの情報収集を行った。

神戸市も含めた兵庫県全域で、新型インフルエンザの確定例(定型・非定型)は6月5日までに199名(男性65.3%、女性34.7%)、15～19歳が71.9%を占め、感染の中心は高校生であった。兵庫県における流行曲線では、5月5日発症の確定患者が初めて検出され、5月17日にピークを形成した後、兵庫県全域で実施された学校休業に伴い症例数は減少した。神戸市で最初の確定例が確認された5月16日には、兵庫県いくつかの地域ですでに確定例が認められた。

初期に入院した患者49人について、発熱、咳、全身倦怠感、咽頭痛を示すものが70%以上に認められた。48例に抗インフルエンザ薬が投与され、1週間以内で症状が軽快するものがほとんどであった。患者の大半は感染症法に基づく入院で、基礎疾患のない若年者に集中しており、人工呼吸管理を要するような重症例は認められなかった。

感染源及び接触日が特定できる事例から、二次感染が疑われる事例は除外して検討したため短めに評価されている可能性があるが、潜伏期は1－4日(中央値2日)と推定された。同居家族全体における発症割合は7.0%であるのに対し、10～19歳では21.6%と高かった。初発患者が発症してから家族内発症者の症状出現まで、中央値3日(範囲1－5日)であった。同居家族における感染者は接触者調査時すでに発病するなどして、予防内服は実施されていなかった。初発患者の症状出現から2日以内に予防投与が開始されたものは29%にとどまったが、予防投与が実施されたものから発症者はなかった。

神戸市環境保健研究所でRT-PCRにより検査された検体の新型インフルエンザ(A/H1N1 pdm)陽性割合は、15-19歳の年齢階級で高かったが、他の年齢層に感染が広大する所見は確認されなかった。

流行の早期探知、重症患者の検出のためのサーベイランスの強化、予防投薬の実施体制の整備、関係機関での情報共有と連携、リスクコミュニケーションによる情報・知識の共有が望まれた。

(2010/1/7 IDSC 更新)

＊情報は日々更新されています。各ページごとにブラウザの「再読み込み」「更新」ボタンを押して最新の情報をごらんください。

パンデミック(H1N1)2009 Pandemic (H1N1)2009

IDSC 更新情報

神戸市および兵庫県における新型インフルエンザ集団発生疫学調査報告

第2部
学校編

2009年8月31日

国立感染症研究所 実地疫学専門家養成コース(FETP)
国立感染症研究所 感染症情報センター

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第2部要約

(1)学校における積極的疫学調査

兵庫県における新型インフルエンザの感染の中心は高校生であった(本報告書第1部を参照)。よって、学校における発生状況を把握し、疫学的特徴を明らかにすることにより感染拡大防止対策につなげることを目的として、確定症例が初期に発生した3つの高校在籍者および教職員(A校/B校/C校)を対象に質問票による積極的疫学調査を行った。3つの学校はほぼ同時期より流行が始まっていたが、それぞれの学校におけるイベントや生徒の活動状態により異なった流行の様相を呈していた。なかでも学校全生徒の集合するイベントが感染拡大には大きな影響を与えていたことが示唆された。

(2)学校休業の記述的評価

積極的疫学調査が実施された3つの学校に加えて、その他の学校においても記述的に学校休業の効果の検討を行った。神戸市の学校における確定症例についての流行曲線より、学校休業は流行の広がりを阻止するのに有効であったと考えられた。

(3)兵庫県における学校間の疫学的リンク

今回の兵庫県において確定症例の発生した学校のうちいくつかの学校は、部活動のつながりで疫学的リンクを説明することが出来た。部活動内でのどのような具体的な行動・活動が、感染拡大に寄与したのかは、調査を行えておらず、不明である。また集団発生のあった大阪の高校とのつながりは不明であった。

(4)学校での感染拡大を防ぐための取りくみ

日常からの感染予防対策の実行、生徒・保護者への感染症知識の提供、校内での異常の早期探知と対応への取り組み、保健所など関係機関との連絡強化が望まれる。

（2010/1/7 IDSC 更新）

＊情報は日々更新されています。各ページごとにブラウザの「再読み込み」「更新」ボタンを押して最新の情報をごらんください。