Cost-effectiveness of influenza control measures: a dynamic transmission model-based analysis

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SUMMARY

We investigated the cost-effectiveness of different influenza control strategies in a school setting in Taiwan. A susceptible-exposure-infected-recovery (SEIR) model was used to simulate influenza transmission and we used a basic reproduction number (R_0)–asymptomatic proportion (θ) control scheme to develop a cost-effectiveness model. Based on our dynamic transmission model and economic evaluation, this study indicated that the optimal cost-effective strategy for all modelling scenarios was a combination of natural ventilation and respiratory masking. The estimated costs were US$10/year per person in winter for one kindergarten student. The cost for hand washing was estimated to be US$32/year per person, which was much lower than that of isolation (US$55/year per person) and vaccination (US$86/year per person) in containing seasonal influenza. Transmission model-based, cost-effectiveness analysis can be a useful tool for providing insight into the impacts of economic factors and health benefits on certain strategies for controlling seasonal influenza.

Key words: Cost-effectiveness analysis, influenza, modelling, control measures, basic reproduction number.

INTRODUCTION

The influenza virus causes widespread morbidity and mortality in various populations: an average of 250 000–500 000 deaths occur every year worldwide [1]. In subtropical regions like Taiwan, this impact is felt predominantly during the winter months, and the epidemics recur with a highly predictable seasonal pattern. Seasonal variation in disease transmission thus plays an important role in the transmission dynamics of influenza. Since schools are centres for the spread of influenza, the probability of disease transmission is considerably higher due to increased mixing level of people during school terms compared to school holidays [2].

Our previous studies [3–5] have focused on both the theoretical and empirical aspects of the transmission dynamics of indoor respiratory infections. These were aimed at both understanding observed epidemiological patterns and predicting the consequences of introduced public health interventions along with effective engineering control measures to contain infectious diseases.

A Wells–Riley mathematical model was employed for modelling indoor respiratory infection [3–5] to

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estimate the exposure concentrations (q) in indoor environments and to estimate the basic reproduction number (R_0) in a shared indoor airspace. Riley *et al.* [6] developed a Wells–Riley mathematical equation to estimate the probability of airborne transmission of an infectious agent indoors. The key parameter is the quantum generation rate (q) of infectious quanta by an infected person. The q value was defined by Wells [7] who conducted a series of experiments to estimate the response and reaction to inhaled infectious droplets, indicating that a quantum (or infectious dose) can infect 63·2% of susceptibles tested. Hence, exposure to one quantum of infection gives an average probability of 63% of becoming infected [7]. The R_0 value is the key epidemiological determinant that characterizes the transmission potential of a disease, which is defined as the average number of successful secondary infection cases generated by a typical primary infected case in an entirely susceptible population [8]. R_0 essentially determines the rate of spread of an epidemic and how intensive a policy will need to be to control the epidemic. $R_0 > 1$ implies that the epidemic is spreading within a population and that incidence is increasing, whereas $R_0 < 1$ means that the disease is dying out. An average $R_0 = 1$ means the disease is in endemic equilibrium within the population.

We also adopted the competing-risks model [9–11] to understand the dynamics of the interplay in different enhanced engineering control measure strategies. The competing-risks model is a probabilistic model by which the dynamics of interplay in different enhanced engineering control-measure strategies can be described. The basic assumption of the probabilistic calculations on the competing-risks model was based on an underlying Poisson model, i.e. different control efficacies act independently of each other. The selected optimal control measures include environmental controls by ventilation and air filtration, as well as respiratory protection. The inclusion of competing risks in the model recognized the fact that an individual might gain substantial benefits in risk reduction of airborne infection from many different control measures including technological controls at the source (by surgical masking and treatment booths), environmental controls (by ventilation, air filtration and ultraviolet germicidal irradiation), and receptor controls (by respiratory protection via respirators) [12–14].

We linked the competing-risks model and Wells–Riley mathematical equation in order to estimate the reduction of the potential infectious force of R_0.

Finally, a susceptible-exposed-infected-recovery (SEIR) model was used for quantitatively explaining the dynamics of an epidemic. However, in our study, we ignored the control measure effectiveness variation and unit cost estimations.

The cost benefits of influenza vaccination were assessed for many countries; the methods of assessment and unit cost of control measures were different in each country [15, 16]. Published studies provide the cost analysis methods and consider the direct (hospitalization or vaccination) and indirect costs (parent work loss) of disease burden for comparison with different scenarios, such as the vaccinated coverage rate [17] and school closure policies of varying length [18]. However, in Taiwan, the major efficacy and cost-effectiveness evaluations of control measures against influenza were focused on vaccination [19, 20]. However, other control measures using engineering approaches [i.e. ventilation, high-efficiency particulate air (HEPA) filtration, and ultraviolet germicidal irradiation (UVGI)], personal protection equipment (i.e. respiratory protection masks), and public health interventions (i.e. isolation and hand washing) were lacking. Thus, it is worthwhile to study the cost-effectiveness analysis of potential control-measure combinations. The control of infectious diseases is often a compromise between the desire for large-scale implementation of control measures and what is logically or economically feasible. The use of cost-effectiveness analysis can help organizations like Medicare to target its healthcare resources more efficiently, and it must be part of a comprehensive strategy [21, 22]. Cost-effectiveness analysis in healthcare involves the identification of all relevant alternative uses of a resource (cost) in concert with the evaluation of expected health gains derived by implementing that resource.

In this paper, we integrated control-measure modelling as a new dimension of cost-effectiveness analysis to systematically quantify the combinations of control-measure efficacies as well as to understand what is required for seasonal-specific influenza control. Thus, the purpose of this study was to examine the potential health outcomes and cost-effectiveness of different combinations of influenza control strategies in a school setting. The results of this study may be used to maximize health benefits per dollar spent and may be used as an aid to rational public health decision making. Policymakers may need information on the epidemiological and economic impact of different potential control-measure combinations,
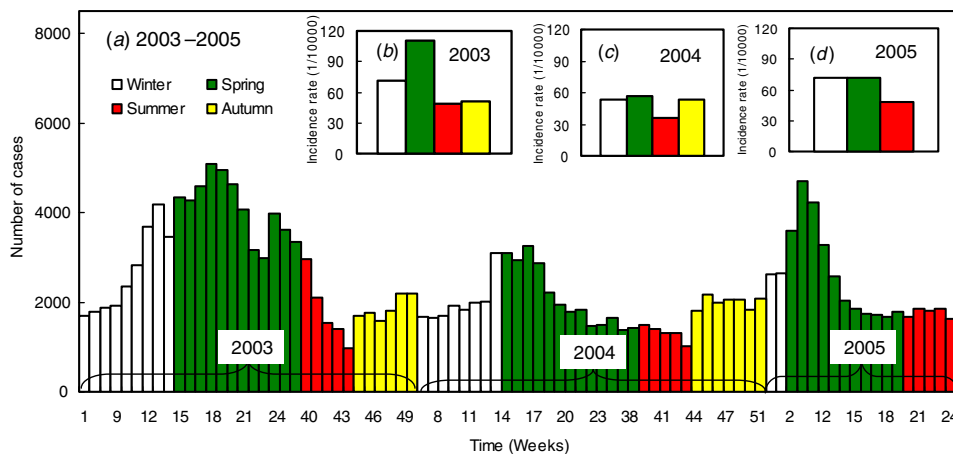
Fig. 1 [*colour online*]. (*a*) Seasonal influenza epidemiological data from 2003 to 2005 in Taiwan. The number of cases of seasonal influenza are illustrated for winter, spring, summer, and autumn, respectively. (*b–d*) represents 2003 to 2005 influenza incidence rates in schoolchildren, respectively.

pertaining to seasonal influenza, in order to formulate tentative guidelines.

MATERIALS AND METHODS

Influenza epidemiology characteristics

Our study was conducted at Ming-Chuan Elementary School located in southern Taipei. A total of 494 students, including 60 kindergarten and 434 elementary students, were housed in four buildings. The school has two kindergarten classes and 19 elementary classes with grades ranging from 1 to 6. Within those classes, schoolchildren were classified into four age groups: kindergarten (aged 4–6 years) and elementary students (7–8, 9–10, 11–12 years). Teaching and administrative staff aged 25–45 years were also included. Detailed descriptions of the study population have been presented in Chen *et al.* [4]. We adopted the elementary school setting based on weekly seasonal influenza epidemiological data from the Taiwan Center for Disease Control (CDC) databank from 2003 to 2005 (http://www.cdc.gov.tw/en/index.asp). We pooled data into spring/winter and summer/autumn to reflect the seasonal average incidences (Fig. 1*a*). The estimated spring average incidence rates were 110·94, 57·03, and 72·07/10 000 persons for 2003, 2004, and 2005, respectively; whereas the winter average incidence rates were estimated as 71·78, 53·50, and 71·49/10 000 persons for 2003, 2004, and 2005, respectively (Fig. 1*b–d*).

Control measure modelling

Here we used a $R_0-\theta$ control curve to formulate the cost-effectiveness analysis, where R_0 represents the basic reproduction number and θ represents the asymptomatic proportion of infected persons. The $R_0-\theta$ control curve, denoted as $R_0=f(\theta)$, can be derived from an equation-based control model [5, 23]. Based on the $R_0-\theta$ control curve, if a given infectious agent localizes below the curve (area A_1), the outbreak is always controlled eventually; however, if an infectious agent localizes above the curve (area A_2), additional control measures would be required to control spread. The uncontrollable ratio (f_{uc}) used to examine the effectiveness of the control measure adopted can be determined from the $R_0=f(\theta)$ curve as (Fig. 2):

$$f_{uc} = \frac{A_2}{A_1 + A_2}, \tag{1}$$

where A_1 and A_2 are areas under (representing the controllable area) and above (representing the uncontrollable area) the $R_0=f(\theta)$ curve, respectively.

Table 1 summarizes the mathematical models used to calculate R_0 with and without control measures and $R_0=f(\theta)$ functions based on different public health interventions. The proposed control measures included engineering approaches such as natural ventilation (G), high-efficiency particulate air (HEPA, H) filtration, and ultraviolet germicidal irradiation (UVGI, U) and personal protection equipment such as utilization of respiratory protection masks (M). The public health interventions were isolation (I), vaccination (V), and hand washing (HW).

Parameter estimates for θ can be determined by the specific biological characteristics of the aetiological agents, where $\theta=$ (incubation period−latent period)/ infectious period. We calculated the distribution of θ

Table 1. *Mathematical expressions for basic reproduction number (R_0) without control measures, with engineering and personal protection control measures, and $R_0 = f(\theta)$ functions with i public health interventions and personal control measures*

R_0 without control measures

$$R_0 = (n-1) \times \left\{ 1 - \exp\left\{ -\frac{Iqpt}{Q}\left\{ 1 - \frac{V}{Qt}\left[1 - \exp\left(-\frac{Qt}{V} \right) \right] \right\} \right\} \right\} \tag{T1}$$

R_0 with engineering and personal protection control measures

$$R_{0E} = (n-1)\left\{ 1 - \exp\left[-\left(\frac{qtp(1-\eta_s)}{Q + \lambda V + Q_r\eta_r} \right)\left(1 - \exp(-(ACH + \lambda + ACH_r\eta_r))t \right) \right] \right\} \tag{T2}$$

$R_0 = f(\theta)$ functions with i public health intervention(s) and personal control measures

$i = 1$

$$R_0 = [(1-\varepsilon_1) + \varepsilon_1\theta]^{-1} \tag{T3}$$

$i = 2$

$$R_0 = \left\{ \left[(1-\varepsilon_1)(1-\varepsilon_2) + \varepsilon_1(1-\varepsilon_2)\theta + (1-\varepsilon_1)\varepsilon_2\theta + \varepsilon_1\varepsilon_2\frac{\theta}{2-\theta} \right] \right\}^{-1} \tag{T4}$$

$i = 3$

$$R_0 = \left\{ \begin{bmatrix} (1-\varepsilon_1)(1-\varepsilon_2)(1-\varepsilon_3) + \varepsilon_1(1-\varepsilon_2)(1-\varepsilon_3)\theta + \varepsilon_2(1-\varepsilon_1)(1-\varepsilon_3)\theta + \varepsilon_3(1-\varepsilon_1)(1-\varepsilon_2)\theta \\ +[\varepsilon_1\varepsilon_2(1-\varepsilon_3) + \varepsilon_1\varepsilon_3(1-\varepsilon_2) + \varepsilon_2\varepsilon_3(1-\varepsilon_1)][\theta/(2-\theta)] + \varepsilon_1\varepsilon_2\varepsilon_3\left(\theta/(3-2\theta) \right) \end{bmatrix} \right\}^{-1} \tag{T5}$$

n is the population size; I is the number of infectors; q is the quantum generation rate by an infected person (quanta/day); p is the breathing rate per person (m^3/day); t is the total exposure time (days); Q is the fresh air supply rate (m^3/day); V is the volume of the ventilated space (m^3); Q_r is the air flow rate through a recirculation HEPA filter (m^3/h); η_δ is the efficiency of respiratory protection masking used by an infected person (dimensionless); η_r is the single-pass removal efficiency for an infectious droplet nuclei passing through the recirculation HEPA filter (dimensionless); ACH is the air change rate (/h); ACH_r is the air change rate through a recirculation HEPA filter (/h); λ is the inactivation rate of an infectious droplet nuclei due to UVGI (/h); and ε_1, ε_2, and ε_3 denote the efficacies of isolation, vaccination, and hand washing, respectively.
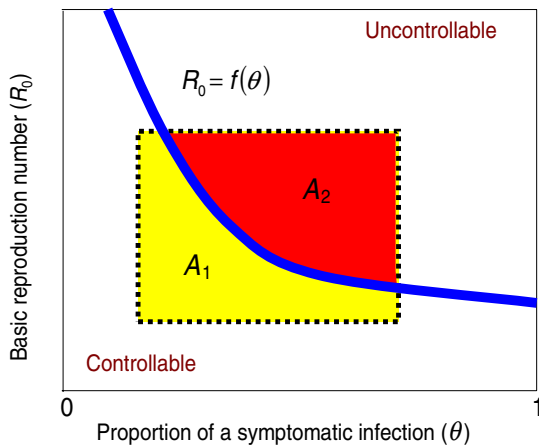

Fig. 2 [*colour online*]. Illustration of the $R_0 - \theta$ criteria for outbreak control. The critical line represents the combination of R_0, θ, and certain efficacies of control measures that can be shown in equations (T3)–(T5) (Table 1).

using the Monte Carlo simulation to quantify the uncertainty concerning θ, which was attributable to the large variance of the incubation, latent, and infectious periods for a specific airborne infection. Utilizing previous work, we were able to obtain range

values for the incubation, latent, and infectious periods as 1–4, 1–3, and 4–8 days, respectively, for influenza [8].

Unit cost estimations

Table 2 summarizes the unit cost per year for engineering control measures, personal protection, and public health interventions. The costs of outpatient treatment were estimated to be US$11.55 per person [22]. The costs of UVGI were separated into equipment (lamp) and consumption (UV) costs. The lifespan of one lamp was estimated to be around 8000–10 000 hours; hence, the costs of UVGI per year were estimated to be US$182. The costs of HEPA filtration were also separated into equipment and consumption costs based on the available market price, resulting in a consumption cost estimated at US$137 per year.

The costs of isolation per year were reasonably assumed to be US$3040 based on expert opinion. The costs of inactivated influenza vaccination per year were estimated by the cost of one vaccine

Table 2. *Unit cost of control measures including engineering, personal protection, and public health interventions*

Control measure	Symbol	Cost factor (US$/person)	Estimated process
Outpatient treatment		11·55	380 NT$ (outpatient treatment cost)/32·9
UVGI	U	182·37	6000 NT$ (Cost per UV lamp)/32·9
HEPA	H	136·78	4500 NT$ (HEPA expendable filer)/32·9
Isolation	I	3040	10 000 NT$ (administrative cost)/32·9
Vaccine	V	4875	18·75 (US$ per vaccine) × 260 (total number in Min-Chung Elementary School)
Respiratory masking	M	27·36 for kindergarten students	15 (NT$ per surgical mask) × 60 (estimated number)/32·9
Hand washing	HW	1605	{[6 (times of hand washing a day) × 1000 c.c./ml (volume of hand washing per time) × 0·01 NT$ (water cost per litre) × 180 (days per year) × 260 persons)] + 50 000 NT$ (administrative cost)}/32·9

UVGI, Ultraviolet germicidal irradiation; HEPA, high-efficiency particulate air; NT$, New Taiwan dollar.
Average exchange rates between NT$ and US$ in March 2007. (https://ebank.bot.com.tw).

(US$12.50) plus the administrative fee (US$6.25), resulting in a cost of US$18.75 per person [21]. The costs of respiratory masking (i.e. using surgical masks) were estimated to be US$27.36 per year based on the 60 masks used per year at Ming-Chung Elementary School. The costs of hand washing were calculated to be US$1605 per year, which was estimated based on the advertised cost of US$1520 plus the cost of water consumption. Detailed descriptions are listed in Table 2.

Cost-effectiveness analysis

Our proposed cost-effectiveness analyses involved four scenarios. Scenario 1 represented no control measures. Scenario 2 represented a combination of engineering approaches and personal protection equipment. Our costs only reflected the outpatient treatment costs due to a lack of information in the questionnaire and other related information such as the costs associated with work loss. Scenario 3 involved a combination of public health interventions and personal protection equipment. Scenario 4 represented several engineering approaches and public health interventions associated with personal protection. Detailed descriptions of the cost estimation for scenarios 1–4 are presented in Appendix 2. Finally, the cost-effectiveness analysis tended to quantify the unit cost per person per year. In other words, we used average cost burden per year divided by all populations (in units of US$/year per person) in order to evaluate the optimal control measures.

RESULTS

Estimates of basic reproduction number

A Wells–Riley mathematical model [equation (T1), Table 1] of indoor respiratory infection [3–5] was employed to estimate the exposure concentrations (q) in indoor environments and to estimate the basic reproduction number (R_0) in a shared indoor airspace. The exposure concentrations (q) were calculated with input parameters of $N = 50$, $V = 600 \text{ m}^3$, $t = 6$ h, $P = 0·38 \text{ m}^3/\text{h}$, $f = 0·00119$, $I = 1$, $P = \text{LN}$ (0·0073, 1·22) and LN (0·0048, 1·44) for winter and summer, respectively (Table 3). The Monte Carlo simulation results show the best fitted lognormal distributions of q with geometric means of 33·92 and 51·62 and geometric standard deviations of 1·14 and 1·22 for summer and winter, respectively.

The box-and-whisker plots of the median basic reproduction numbers (R_0) were estimated to be 3·22, 2·14, 1·71, 2·15, 2·85 for summer and 7·32, 3·78, 4·30, 5·43, 5·98 for winter, respectively, for the five age groups at Ming-Chuan Elementary School (Fig. 3a, b). Figure 3(c, d) shows the median risks of infection (P) in the five age groups for summer and winter, respectively. Grades 5 and 6 gave the highest risk of infection for all seasons. Kindergarten had the highest R_0 estimates, implicating that the density of the population affects age group-specific R_0.

Table 3. *Input parameters used in the Wells–Riley mathematical equation for five age groups in an elementary school*

Age group years	Persons in the ventilated airspace n	No. of infectors i	Volume of the shared airspace V (m³)*	Total exposure time t (days)*	Breathing rate P (m/day)†	Ventilation rate (winter–summer) Q (m³/day)‡
Kindergarten						
4–6	60	1	1013	0·28	N (7·68, 0·15)	48 628–97 257
First and second grades						
7–8	30	1	245	0·25	N (8·4, 0·08)	17 614–35 228
Third and fourth grades						
9–10	23	1	245	0·25	N (9·12, 0·16)	17 614–35 228
Fifth and sixth grades						
11–12	26	1	245	0·25	N (10·56, 0·08)	17 614–35 228
Staff and administrative staff						
25–45	40	1	732	0·11	N (11·16, 0·20)	52 704–105 408

* Estimated from the measurement and course programme at Ming-Chuan Elementary School.
† Adopted from ICRP [30].
‡ Assuming that the ACH = 2–3/h and 4–6/h for kindergarten students and other age groups, respectively.

Predicting the effects of engineering and personal protection

We used equation (T2) (Table 1) to calculate the basic reproduction number (R_{0E}) under multiple engineering and personal protection control measures. We inputted the inactivation rate of infectious droplets due to UVGI (λ = 12/h) [24], single-pass removal efficiency for infectious droplet nuclei passing through the recirculation HEPA filter (η_r = 99·97%), and air change rate through a recirculation HEPA filter (Q_r = 3·499 m³/h) into equation (T2).

The effects of engineering and personal protection are shown in Figure 4. For one control measure (G, natural ventilation) in winter, the median R_{0E} estimates notably decreased from 7·32, 4·5, and 5·98 (Fig. 3b) to 1·35, 2·11, and 1·33 (Fig. 4b) for kindergarten, elementary, and staff and administrative staff, respectively. For two control measures, it produced an order of G+U > G+M > G+H. Finally, using combinations of G+M+H, G+M+U, and G+H+U produced an order of efficacy of G+M+U > G+H+U > G+M+H (Fig. 4).

Effectiveness of public health interventions and personal protection

Table 4 summarizes the available published effectiveness data for inactivated influenza vaccination (V), hand washing (HW), and isolation (I). We deduced that the average vaccination effectiveness estimates were 0·70, 0·62, and 0·50 with standard deviations of 0·06, 0·06, and 0·03 for children, adults, and the elderly, respectively, by using 10 000 Monte Carlo simulations. On the other hand, the average effectiveness of hand washing and isolation were estimated to be 0·24 and 0·82 with standard deviations of 0·03 and 0·06, respectively.

The impact of the different combinations of public health interventions (V, HW, I) were assessed by $R_0 - \theta$ control models [equations (T3)–(T5)] (Table 1). Parameter estimates for θ of influenza were determined by the specific biological characteristics of the aetiological agents. The uniform distributions [represented as mean (min-max)] that best fit the incubation, latent, and infectious periods were estimated to be 2·5 (1·0–4·0), 2·0 (1·0–3·0), and 6·0 (4·0–8·0) days, respectively. In the uniform distribution, all values between the minimum and maximum occur with equal likelihood. Hence, we assumed the ranges were minimum and maximum and all values between the minimum and maximum occur with equal likelihood. The 95% confidence intervals (CIs) for the proportion of people with asymptomatic infection ranged from 0·19 to 0·44 by the definition of θ. Finally, Figure 5 shows that the effectiveness of public health intervention followed the order of I > V > HW and I+V > I+HW > V+HW across all age groups, indicating that isolation had the greatest effect on influenza control without considering the cost effects.
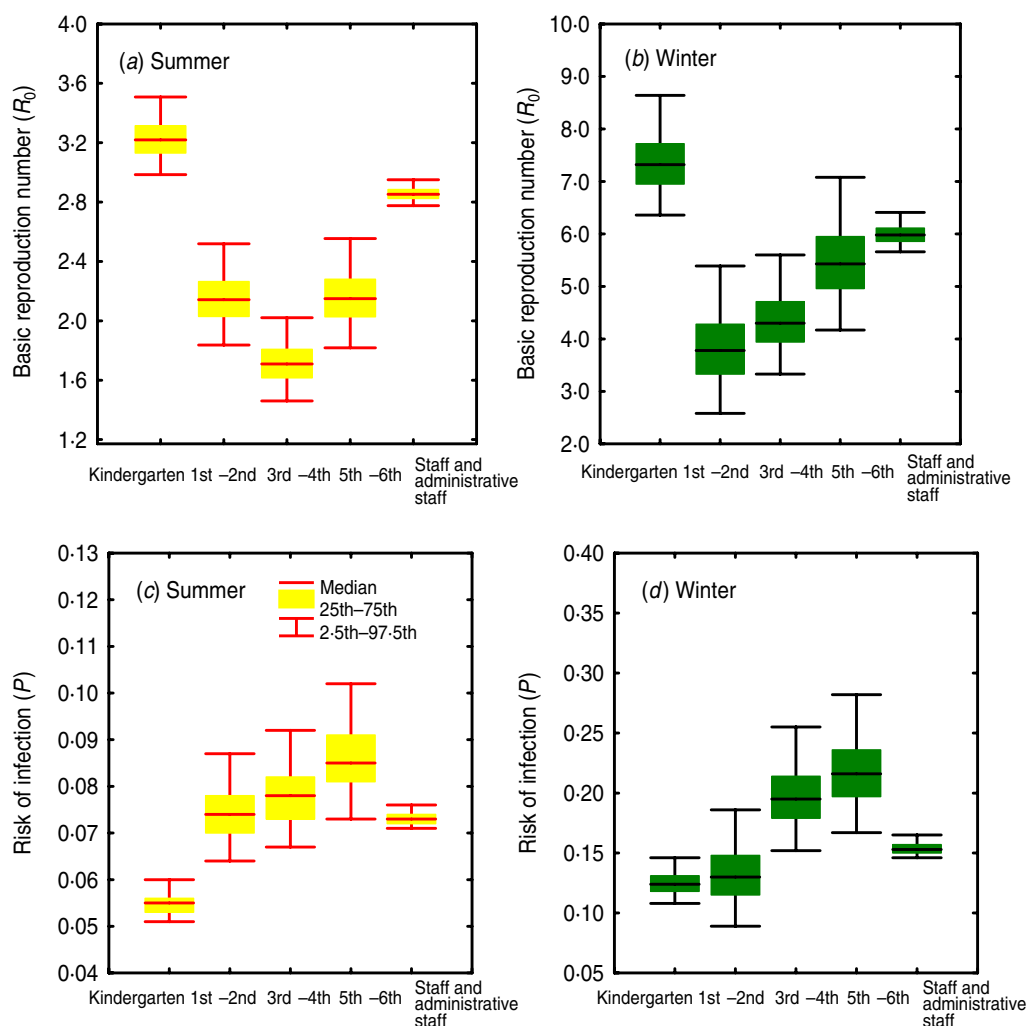
Fig. 3 [colour online]. (a, b) Box-and-whisker plots of the seasonal basic reproduction number (R_0) and (c, d) risk of infection (P) for summer and winter, respectively. Five age groups, including kindergarten, grades 1–2, 3–4, and 5–6, and staff/administrative staff, respectively, are defined.

Cost-effectiveness analysis

Cost-effectiveness analysis for scenario 1 is presented in Figure 6(a, b). The box-and-whisker plots without any control measures in summer show that the average cost for a kindergarten student was US$2.64/year per person (95% CI 2·39–2·84), indicating that the costs are higher than those of elementary students (US$1.40/year per person; 95% CI 1·00–1·85) and teaching and administrative staff (US$2.32/year per person; 95% CI 2·23–2·40) (Fig. 6a). Similarly, the costs for kindergarten students in winter (US$4.5/year per person; 95% CI 4·23–4·77) were also higher than those of elementary students (US$3.4/yr per person; 95% CI 2·69–4·13) and teaching and administrative staff (US$4.13/year per person; 95% CI 4·01–4·27) (Fig. 6b). The costs in winter were 41% higher than in summer for the kindergarten age group.

Cost-effectiveness analysis for scenario 2 was estimated to be US$0.67 (G+M), US$3.23 (G+U), and US$3.92/year per person (G+H) for kindergarten students (Fig. 6c). Costs in winter were 68%, 10%, and 30% higher than those in summer for kindergarten students for the G+M, G+U, and G+H combinations, respectively (Fig. 6d). For cost-effectiveness analysis in scenario 3, the results showed that US$31.25/year per person for hand washing was the highest cost-effectiveness control measure compared to isolation (US$55.16/year per person) and vaccination (US$85.75/year per person) (Fig. 7).

DISCUSSION

This study attempted to examine the potential health outcomes and cost-effectiveness of different
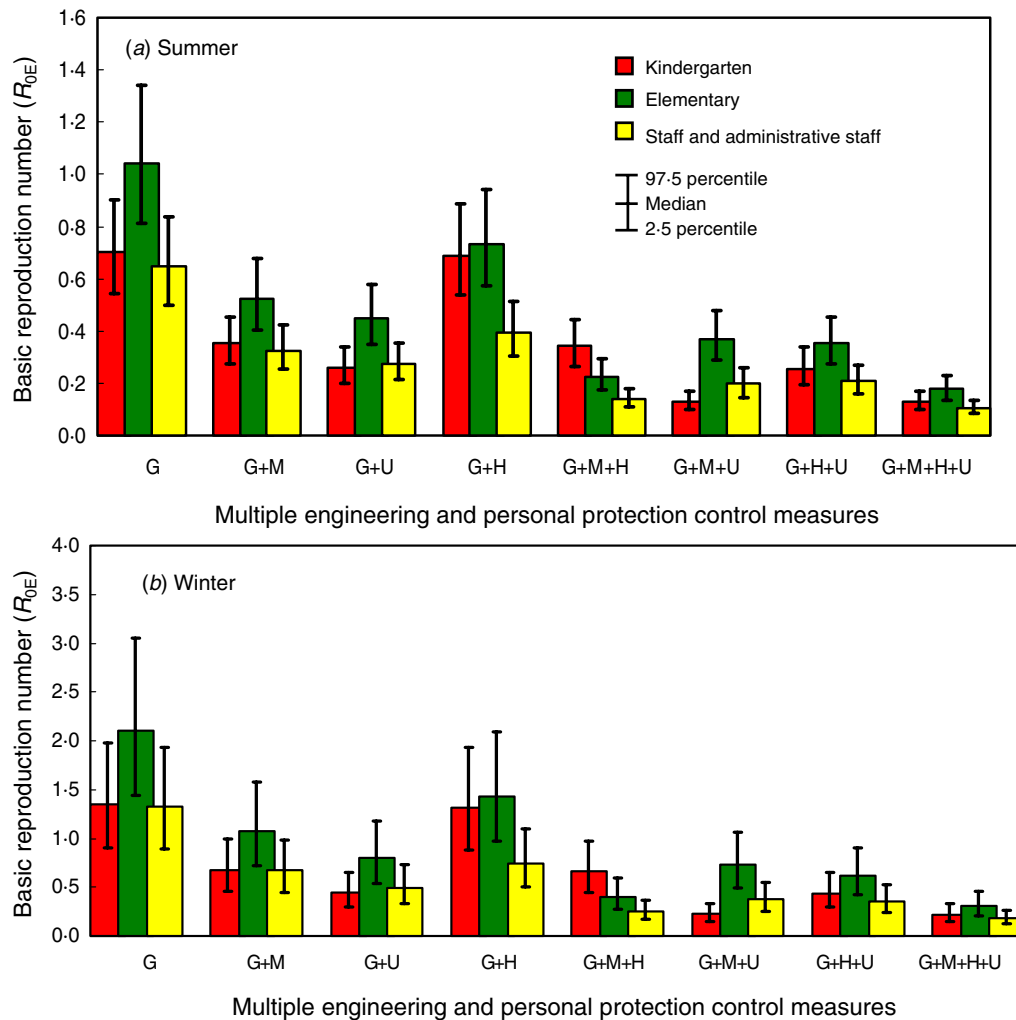
Fig. 4 [*colour online*]. Under multiple control measures of natural ventilation (G), respiratory masking (M), ultraviolet germicidal irradiation (UVGI, U), and high-efficiency particulate air (HEPA, H) filtration, estimates of seasonal R_{0E} were produced and are shown for (*a*) summer and (*b*) winter. Three age groups of kindergarten, elementary students, and staff/administrative staff are included.

combinations of influenza control strategies in a school setting. This information may be useful to maximize the health benefits per dollar spent and can be used as an aid to rational public health decision making.

We found a set of intervention strategies that gave the highest reduction in basic reproductive number. For multiple engineering approaches and personal control measures, G+M+H+U strategies were the most effective interventions with a corresponding R_{0E} estimate of 0·22 (95% CI 0·15–0·33) for kindergarten students in winter. G+U and G+M+U strategies had an R_{0E} estimation of 0·45 (95% CI 0·30–0·66) and 0·22 (95% CI 0·15–0·33), respectively (Fig. 4b). For multiple public health interventions, the R_0 estimates for kindergarten students in winter

decreased to 6·88 (95% CI 5·98–8·12), 7·19 (95% CI 6·25–8·49), and 7·32 (95% CI 6·36–8·64) for I+V+HW, I+V, and I+HW, respectively [equations (T3)–(T5)]. Regarding our dynamic transmission model and economic evaluation, this study indicated that the optimal cost-effective strategy for all scenarios was the combination of natural ventilation and respiratory masking. The estimated costs were US $10/year per person in winter for one kindergarten student. The cost for hand washing was estimated to be US$32/year per person, which was much lower than isolation (US$55/year per person) and vaccination (US$86/year per person) costs in containing seasonal influenza.

The main strength of this study was that it provides a new perspective on methods to integrate the

Table 4. *Published effectiveness (median with 95% confidence interval) of selected public health interventions of vaccination, hand washing, and isolation*

Population	Outcome studied	Effectiveness*	Ref.
Inactivated influenza vaccination effectiveness			
Children (3–14 yr)	Influenza-like illness	0·75 (0·61–0·84)	[31]
	Influenza A cases confirmed by PCR	0·88 (0·49–0·97)	[31]
Children (6 months–17 years)	Vaccine effectiveness in preventing influenza illness	0·69 (0·40–0·90)	[29]
Healthy adults	Culture positive	0·77 (0·37–0·92)	[32]
	Real-time PCR positive	0·74 (0·37–0·89)	[32]
	Culture or real-time PCR positive	0·75 (0·42–0·90)	[32]
	Serological positive	0·78 (0·37–0·93)	[32]
	Culture or serological positive	0·67 (0·16–0·87)	[32]
Community-dwelling elderly	Hospitalizations (respiratory conditions)	0·32 (0·29–0·40)	[32]
	Deaths from all cases	0·50 (0·45–0·56)	[32]
Elderly in nursing homes	Respiratory illness	0·56 (0·39–0·68)	[32]
	Hospitalizations	0·48 (0·28–0·65)	[32]
	Deaths	0·68 (0·56–0·76)	[32]
Hand washing effectiveness			
	Relative risk		
	1·37 (0·78–2·40)	0·27 (0–0·58)	[33]
	1·25 (0·81–1·92)	0·20 (0–0·48)	[34]
	1·06 (0·78–1·44)	0·06 (0–0·31)	[33]
	1·47 (1·01–2·13)	0·32 (0·009–0·53)	[35]
	1·12 (1·03–1·22)	0·11 (0·029–0·18)	[36]
	1·80 (1·78–1·82)	0·45 (0·438–0·45)	[37]
	1·34 (0·96–1·89)	0·25 (0–0·47)	[38]
	1·25 (1·14–1·37)	0·20 (0·12–0·27)	[39]
Isolation effectiveness			
		0·88 (0·9–0·75)	[40]

PCR, Polymerase chain reaction.
* Effectiveness $= 1 - (1/\text{relative risks}) \times 100\%$ [40].

maximum estimation for infected numbers of people, unit cost of outpatients, and cost estimations of control measures. We used the $R_0=f(\theta)$ function to describe the control impact on the basic reproduction number (R_0) through the use of isolation, vaccination, and hand washing. This study also simulated engineering approaches (using HEPA filtration and UVGI) and respiratory protection masking in a school setting by use of a modified Wells–Riley equation. Most cost-effectiveness studies are focused on vaccination of high-risk populations, including the elderly [21, 25–27] and children [28, 29], because many countries have an established Medicare system, and hospital databases that can offer methods to evaluate the (in)direct costs when influenza vaccination is adopted. Many of these studies did not consider the effects of engineering approaches or respiratory protection masking on cost-effectiveness analysis for influenza epidemics. For seasonal-specific analysis, results indicate that it was not possible to provide an exact prediction of cost-effectiveness because several model inputs were uncertain. For example, the frequency of hand washing in 1 day or the cost per 1 litre of water was variable. Other model inputs such as the replacement frequency of respiratory masks and the types of masks used were different. There are two limitations to our study. A potential weakness of the analysis was that it only considered the costs of outpatient treatment for people who became infected. The indirect costs for work and productivity loss, even the hospitalization costs that arise from illness, were not taken into account. Hence, the burden of disease could be underestimated in our study. In other words, the total costs for each scenario were largely derived from the costs of control measures and not the costs of outpatient treatment. The second potential weakness of our study is that engineering methods may not be feasible. Natural ventilation represents a cost-effective approach; however, the ventilation conditions were not easy to quantitate and adjust.
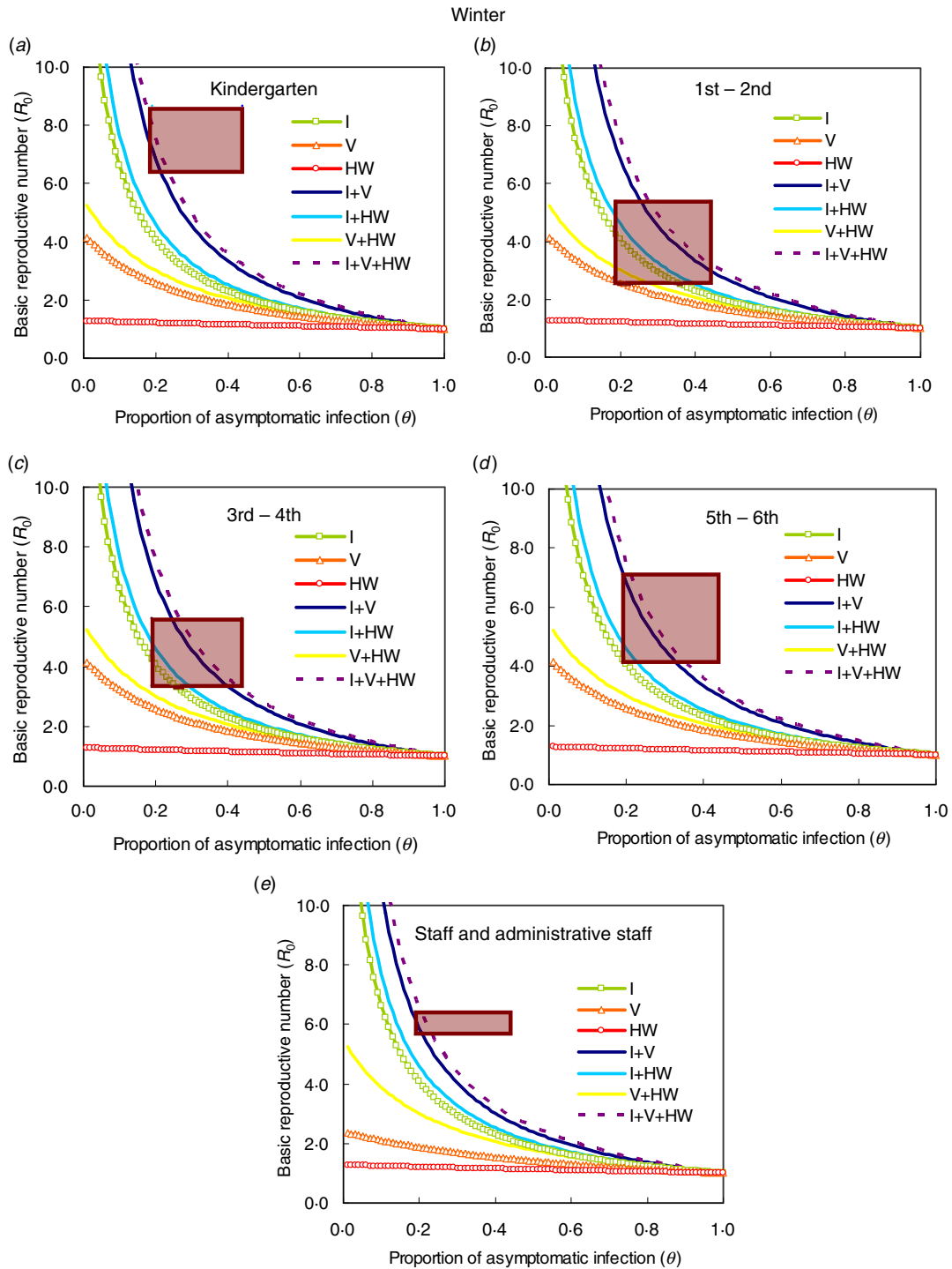
Winter

Fig. 5 [*colour online*]. Modelling the impact of the combinations of public health intervention and personal protection, including isolation (I), vaccination (V), and hand washing (HW). Panels (*a*)–(*e*) represent the five age groups of the R_0–θ critical control model based on I, V, HW, I+V, I+HW, V+HW, and I+V+HW in winter and associated with the estimates of the basic reproduction number (R_0) and the proportion of asymptomatic infection (θ).

In conclusion, this study provides important baseline information on the costs and effectiveness of control strategies that can be used to judge the overall impact of communicable disease on the health of the population. For seasonal-specific cost-effectiveness analysis, the cost in winter was slightly higher than in summer, implying that we need more efforts on school health promotion programmes in the winter
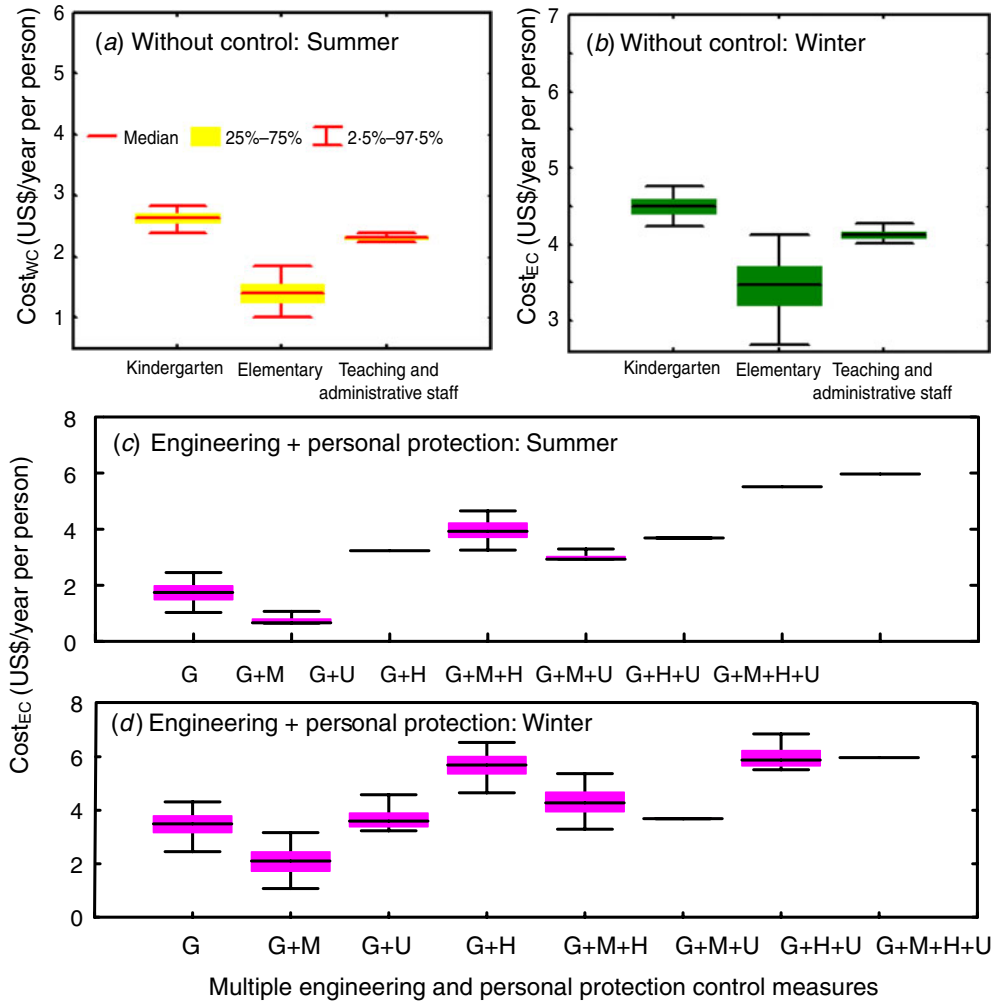
Fig. 6 [*colour online*]. (*a, b*) Cost-effectiveness analyses for scenario 1 (without any control measures) for the three age groups of kindergarten, elementary, and staff/administrative staff. (*c, d*) Cost-effectiveness analysis for scenario 2 (multiple engineering and personal protection control measures) are presented.

season. Our study also demonstrates that model-based, cost-effectiveness analysis can be useful to explore infectious disease trends and health consequences of interventions in a population over time, providing insight into the impacts of economic factors and health benefits on certain prevention combinations against seasonal influenza transmission. In the future, cost-effectiveness analysis must be part of a comprehensive strategy that involves changing incentives at multiple levels.

APPENDIX 1. The SEIR model

The parameters S, E, I, and R were used for the epidemiological classes. The SEIR model can provide a basic description of the transmission dynamics of

pandemic influenza by using a simple parameterized set of ordinary differential equations:

$$\frac{dS}{dt} = \mu N - \beta IS - \mu S, \tag{A1}$$

$$\frac{dE}{dt} = \beta IS - \sigma E - \mu E, \tag{A2}$$

$$\frac{dI}{dt} = \sigma E - \upsilon I - \mu I, \tag{A3}$$

$$\frac{dR}{dt} = \upsilon I - \mu R, \tag{A4}$$

$$N(t) = S(t) + E(t) + I(t) + R(t), \tag{A5}$$

where $N(t)$, $S(t)$, $E(t)$, $I(t)$, and $R(t)$ represent the number of total persons, susceptible, exposed, infected, and recovered at time t for specific age groups, respectively. β represents the transmission coefficient for the probability that an infected person will have contact with and successfully infect a susceptible
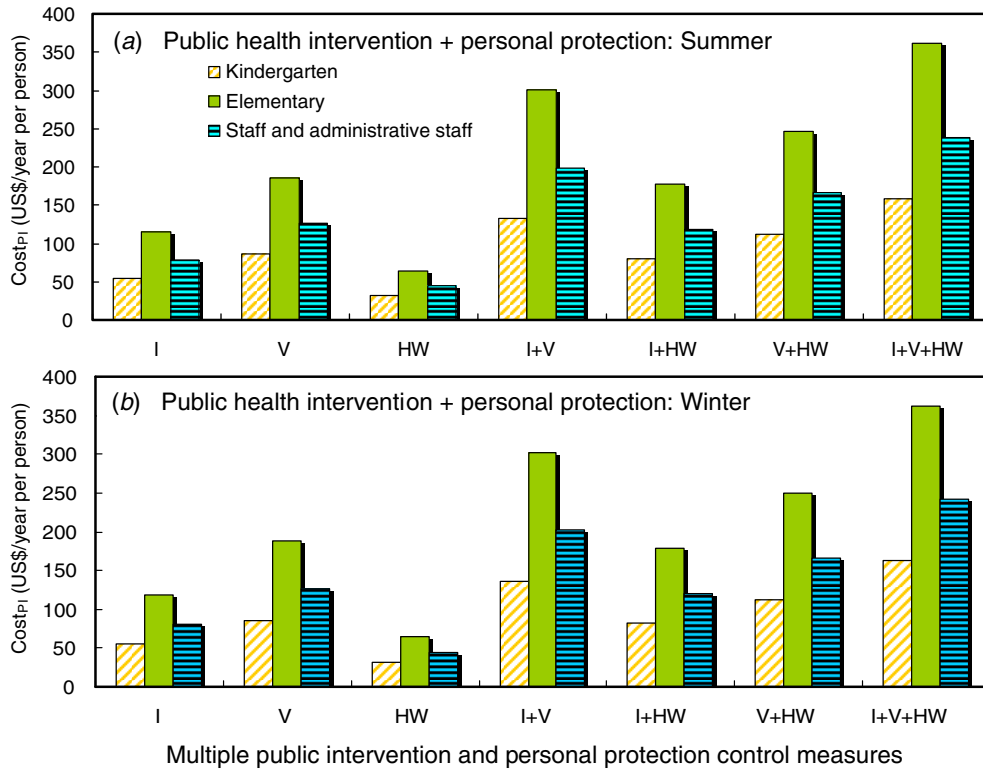
Fig. 7 [*colour online*]. (*a*) Cost-effectiveness analysis for scenario 3 (multiple public health intervention and personal protection control measures) in summer and winter for the three age groups, respectively.

person, which can be estimated by $R_0 = (\beta \times N)/(\mu + \upsilon)$ [8]. σ represents the rate at which an exposed individual becomes infectious per unit time, which is equal to 0·333/day [8]. υ represents the rate at which an infectious individual recovers per unit time (per day) and is equal to 0·143 (1/average infectiousness periods of 7 days). μ represents the birth rate and death rate, which is equal to 0·013/year (http://www.mio.gov.tw/stat/).

APPENDIX 2. Cost estimations for scenarios 1–4

The costs (in US$/year per person) for scenario 1 (cost$_{WC}$) and scenario 2 (cost$_{EC}$) are represented as:

$$\text{cost}_{wc} = I_{\max-WC} \times C_f, \tag{A6}$$

$$\text{cost}_{EC} = C_{EC} + (I_{\max-EC} \times C_f), \tag{A7}$$

where $I_{\max-WC}$ and $I_{\max-EC}$ represent the maximum infected number of people without intervention and with intervention (engineering and personal protection control), respectively. C_f represents the unit cost per person of the outpatient treatment. C_{EC} represents the cost associated with the combination of engineering and personal protection control strategies. The estimated basic reproduction numbers in scenarios 1

and 2 are respectively denoted as R_0 and R_{0E}. A classic SEIR model (see Appendix 1) can be used to estimate the maximum infected number in a population ($I_{\max}$).

The costs in scenarios 3 and 4 are given as:

$$\text{cost}_{PI} = C_{PI} + (I_{\max-PI} \times C_f), \tag{A8}$$

$$\text{cost}_{PE} = C_{EC} + C_{PI} + (I_{\max-PE} \times C_f), \tag{A9}$$

where $I_{\max-PI}$ is the maximum infected number of people with intervention (public health interventions and personal protection strategies). C_{PI} represents the cost of specific public health interventions and personal protection in a population. For scenario 3, R_0 estimates can be obtained based on $R_0 = f(\theta)$ functions as varied with different public health interventions and personal protection as: $R_0 \times f_{uc}$. For scenario 4, the total costs of control measure combinations (cost$_{PE}$) are given in equation (A9). The $I_{\max-PE}$ is the maximum infected number of people with intervention (public health interventions and the combination of engineering and personal protection controls). R_0 estimates can then be estimated from $R_{0E} \times f_{uc}$.

DECLARATION OF INTEREST

None.

REFERENCES

1. **World Health Organization.** World Health Organization (WHO) website influenza fact sheet (http://www.who.int/mediacentre/factsheets/fs211/en/index.html), 2009.
2. **Ridenhour BJ, et al.** Controlling the spread of disease in schools. *PLoS One* 2011; **6**: e29640.
3. **Liao CM, Chang CF, Liang HM.** A probabilistic transmission dynamic model to assess indoor airborne infection risks. *Risk Analysis* 2005; **25**: 1097–1107.
4. **Chen SC, Chang CF, Liao CM.** Predictive models of control strategies involved in containing indoor airborne infections. *Indoor Air* 2006; **16**: 469–481.
5. **Chen SC, Liao CM.** Modelling control measures to reduce the impact of pandemic influenza among school-children. *Epidemiology and Infection* 2008; **136**: 1035–1045.
6. **Riley EC, Murphy G, Riley RL.** Airborne spread of measles in a suburban elementary-school. *American Journal of Epidemiology* 1978; **107**: 421–432.
7. **Wells WF.** *Airborne Contagion and Air Hygiene.* Cambridge, MA: Harvard University Press, 1955.
8. **Anderson RM, May RM.** *Infectious Diseases of Humans: Dynamics and Control.* UK: Oxford University Press, 1991.
9. **Brookmeyer R, Johnson E, Bollinger R.** Modeling the optimum duration of antibiotic prophylaxis in an anthrax outbreak. *Proceedings of the National Academy of Sciences USA* 2003; **100**: 10129–10132.
10. **Brookmeyer R, Johnson E, Bollinger R.** Public health vaccination policies for containing an anthrax outbreak. *Nature* 2004; **432**: 901–904.
11. **Brookmeyer R, Johnson E, Barry S.** Modeling the incubation period of anthrax. *Statistics in Medicine* 2005; **24**: 531–542.
12. **Nardell EA, et al.** Airborne infection: theoretical limits of protection achievable by building ventilation. *American Review of Respiratory Disease* 1991; **144**: 302–306.
13. **Barnhart S, et al.** Tuberculosis in health care settings and the estimated benefits of engineering controls and respiratory protection. *Journal of Occupational and Environmental Medicine* 1997; **39**: 849–854.
14. **Rudnick SN, Milton DK.** Risk of indoor airborne infection transmission estimated from carbon dioxide concentration. *Indoor Air* 2003; **13**: 237–245.
15. **Baguelin M, et al.** Health and economic impact of the seasonal influenza vaccination programme in England. *Vaccine* 2012; **30**: 3459–3462.
16. **Velasco RP, et al.** Systematic review of economic evaluations of preparedness strategies and interventions against influenza pandemics. *PLoS One* 2012; **7**: e30333.
17. **Acedo L, et al.** Cost analysis of a vaccination strategy for respiratory syncytial virus (RSV) in a network model. *Mathematical and Computer Modelling* 2010; **52**: 1016–1022.
18. **Brown ST, et al.** Would school closure for the 2009 H1N1 influenza epidemic have been worth the cost?: a computational simulation of Pennsylvania. *BMC Public Health* 2011; **11**: 353.
19. **Wang CS, Wang ST, Chou P.** Efficacy and cost-effectiveness of influenza vaccination of the elderly in a densely populated and unvaccinated community. *Vaccine* 2002; **20**: 2494–2499.
20. **Wang ST, et al.** Economic evaluation of vaccination against influenza in the elderly: an experience from a population-based influenza vaccination program in Taiwan. *Vaccine* 2005; **23**: 1973–1980.
21. **Edmunds WJ, Medley GF, Nokes DJ.** Evaluating the cost-effectiveness of vaccination programmes: A dynamic perspective. *Statistics in Medicine* 1999; **18**: 3263–3282.
22. **Neumann PJ, Rosen AB, Weinstein MC.** Medicare and cost-effectiveness analysis. *New England Journal of Medicine* 2005; **353**: 1516–1522.
23. **Fraser C, et al.** Factors that make an infectious disease outbreak controllable. *Proceedings of the National Academy of Sciences USA* 2004; **101**: 6146–6151.
24. **Beggs CB, et al.** Methodology for determining the susceptibility of airborne microorganisms to irradiation by an upper-room UVGI system. *Journal of Aerosol Science* 2006; **37**: 885–902.
25. **Maciosek MV, et al.** Influenza vaccination: health impact and cost effectiveness among adults aged 50 to 64 and 65 and older. *American Journal of Preventive Medicine* 2006; **31**: 72–79.
26. **Aballea S, et al.** The cost effectiveness of influenza vaccination for adults aged 50 to 64 years: a model-based analysis for Spain. *Vaccine* 2007; **25**: 6900–6910.
27. **Hoshi SL, et al.** Cost-effectiveness analysis of influenza vaccination for people aged 65 and over in Japan. *Vaccine* 2007; **25**: 6511–6521.
28. **Weycker D, et al.** Population-wide benefits of routine vaccination of children against influenza. *Vaccine* 2005; **23**: 1284–1293.
29. **Prosser LA, et al.** Health benefits, risks, and cost-effectiveness of influenza vaccination of children. *Emerging Infectious Diseases* 2006; **12**: 1548–1558.
30. **ICRP.** Human respiratory tract model for radiological protection, a report of the task group of the International Commission on Radiological Protection. ICRP Publication, vol. 66. New York: Elsevier, 1994.
31. **Salleras L, et al.** Effectiveness of virosomal subunit influenza vaccine in preventing influenza-related illnesses and its social and economic consequences in children aged 3–14 years: a prospective cohort study. *Vaccine* 2006; **24**: 6638–6642.
32. **Ohmit SE, et al.** Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. *New England Journal of Medicine* 2006; **24**: 2513–2522.
33. **Master D, Longe SH, Dickson H.** Scheduled hand washing in an elementary school population. *Family Medicine Journal* 1997; **29**: 336–339.

34. **Ladegaard MB, Stage V.** Hand-hygiene and sickness among small children attending day care centers. An intervention study. *Ugeskrift for Laeger* 1999; **161**: 4396–4400.

35. **Niffenegger JP.** Proper handwashing promotes wellness in child care. *Journal of Pediatric Health Care* 1997; **11**: 26–31.

36. **Roberts MG, Tobias MI.** Predicting and preventing measles epidemics in New Zealand: application of mathematical model. *Epidemiology and Infection* 2000; **124**: 279–287.

37. **Ryan MA, Christian RS, Wohlrabe J.** Handwashing and respiratory illness among young adults in military training. *American Journal of Preventive Medicine* 2001; **21**: 79–83.

38. **White CG, *et al.*** Reduction of illness absenteeism in elementary schools using an alcohol-free instant hand sanitizer. *Journal of School Nursing* 2001; **17**: 258–265.

39. **White C, *et al.*** The effect of hand hygiene on illness rate among students in university residence halls. *American Journal of Infection Control* 2003; **31**: 364–370.

40. **Jefferson T, *et al.*** Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. *Lancet* 2005; **165**: 265–272.