Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study assessed the economics of stockpiling neuraminidase inhibitors (NIs), which are influenza-specific anti-viral agents, in preparation for pandemic influenza. Specifically, the study examined the use of oseltamivir. The study compared three strategies, the first of which was no action (supportive management of influenza). The remaining two strategies were early treatment of clinical influenza with NIs (treatment only) and prophylaxis in addition to early treatment (prophylaxis).

Type of intervention
Primary prevention and treatment.

Economic study type
Cost-effectiveness analysis and cost-benefit analysis.

Study population
The study population comprised Singapore's 2004 midyear population.

Setting
The setting was community care. The economic study was carried out in Singapore.

Dates to which data relate
The effectiveness data referred to 1918 to 2004, while the resource use data referred to 1996 to 2003. The price year was 2004.

Source of effectiveness data
The effectiveness data were derived from a review of published studies.

Modelling
A decision-analytic model was used to calculate the lifetime costs and health outcomes of the alternative stockpile and treatment strategies. The model was used to estimate the number of infections, the number of fatal hospitalisations, the number of nonfatal hospitalisations, and the number of non-hospitalised patients who recover from influenza.

Outcomes assessed in the review
The outcomes assessed in the review included:

the proportion of the population at high risk from influenza infection due to co-morbidities such as asthma,
the baseline influenza-like illness rate,
the influenza clinical attack rate,
the case-fatality rate,
the hospitalisation rate,
the efficacy of prophylaxis, and
the proportion of the population who would have immunity following prophylaxis.

Study designs and other criteria for inclusion in the review
The authors reported little detail about the methods used in the review of the literature. They stated that they relied upon international studies for the effectiveness of oseltamivir.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
The review included 26 primary studies, as well as data from the Ministry of Health and local physicians.

Methods of combining primary studies
Where multiple estimates were available for a single model parameter, the maximum and minimum values were used in defining a triangular distribution around the selected base value.

Investigation of differences between primary studies
Not reported.

Results of the review
The efficacy of prophylaxis was 70% (range: 50 to 90).

The rate of immunity after prophylaxis was 35% (range: 20 to 50).

The influenza clinical attack rate was 30% (range: 10 to 50).

For persons aged 19 years or younger, the case-fatality rate was 5/100,000 (range: 1 to 12.5) in low-risk persons and 137/100,000 (range: 12.6 to 765) in high-risk persons.

For persons aged between 20 and 64 years, the case-fatality rate was 6/100,000 (range: 1 to 9) in low-risk persons and 149/100,000 (range: 10 to 570) in high-risk persons.
For persons aged 65 years or older, the case-fatality rate was 340/100,000 (range: 28 to 680) in low-risk persons and 1,700/100,000 (range: 276 to 3,400) in high-risk persons.

**Measure of benefits used in the economic analysis**
The measure of benefits used was the life-years saved. Monetary benefits were used in the cost-benefit analysis. The monetary benefits were calculated based on the net present value of future earnings for average-aged persons in the respective age groups (19 or younger, between 20 and 64, or 65 and older), adjusted for age (human capital approach).

**Direct costs**
All direct health care costs were included. The cost data were derived from published studies and were used in a decision analytic model to calculate the population costs of the alternative treatment strategies. The unit costs were derived from the Ministry of Health and local physicians, and so may represent charges rather than the true opportunity cost of the resources used. Although the timeframe for the analysis was greater than 1 year, discounting does not appear to have been undertaken. The study reported the average costs. The study reported the resource use quantities and the costs separately. The authors omitted the costs of side effects from treatment with oseltamivir as these would be small in relation to the costs of pandemic illnesses and deaths. This assumption will favour strategies that include oseltamivir.

**Statistical analysis of costs**
As individual patient-level data were not available, a statistical analysis was not possible.

**Indirect Costs**
The indirect costs were included in the analysis, which was appropriate given the societal perspective. The costs of days or work lost due to illness or caring for an ill relative were valued at SGD 166 and SGD 108, respectively, although what these costs represent was not apparent in the present study. The number of days lost and cost estimates were derived from published studies, as well as data from the Ministry of Health. The authors stated that "individual economic value was calculated from the net present value of future earnings for average-aged persons in the respective age groups adjusted for age". The discount rate applied was not stated.

**Currency**
Singapore dollars (SGD). An exchange rate of 1 US dollar to SGD 1.6908 was used for the price year 2004.

**Sensitivity analysis**
The authors used triangular distributions to characterise the uncertainty around the model inputs. A Monte Carlo simulation was then used to propagate this uncertainty through the study results. The cost data appear to have been treated as point estimates, while the resource use data and effectiveness data were allowed to vary in a probabilistic sensitivity analysis. The authors also conducted a one-way sensitivity analysis to determine the optimal percentage of the population that needed to be covered by NI stockpiles. Further threshold analyses on selected parameters were conducted.

**Estimated benefits used in the economic analysis**
The treatment only strategy was estimated to save 423 lives (range: 183 to 756) compared with no treatment.

Compared with no treatment, prophylaxis of 6 weeks’ duration was estimated to save 492 lives (range: 216 to 870) while prophylaxis of 24 weeks’ duration was estimated to save 903 lives (range: 425 to 1,509).

The side effects of treatment were omitted from the analysis.
Cost results
Stockpiling costs were estimated to be SGD 79 million for treatment only, SGD 631 for prophylaxis of 6 weeks’ duration, and SGD 2,287 for prophylaxis of 24 weeks’ duration. Although the analysis had a lifetime horizon, the costs do not appear to have been discounted.

Synthesis of costs and benefits
The costs and health benefits were combined to calculate the cost per life saved and net economic benefit. Treatment only dominated no action in terms of the cost per life-year saved and resulted in an additional economic benefit of SGD 379 million (range: 89 to 734 million). Prophylaxis of 6 weeks’ duration cost SGD 224,600,000 (range: 81,100,000 to 467,600,000) per life saved compared with no action and resulted in a loss of economic benefit of SGD 487 million (range: -925 to 48 million).

Authors’ conclusions
Treatment only was always beneficial in comparison with no action. The authors calculated that the optimal stockpile is between 40 and 60%, and that prophylaxis is only economically beneficial if it is restricted to high-risk sub-groups.

CRD COMMENTARY - Selection of comparators
"No action" was chosen as a comparator explicitly to represent current practice in the study setting. The focus on oseltamivir as the NI of choice was based on data availability and the safety profile of the drug. There may be alternative relevant NIs with different cost efficacy and safety profiles. You must decide whether the comparisons made in this study are relevant in your own setting.

Validity of estimate of measure of effectiveness
The estimate of effectiveness was derived from a review of published studies. The authors did not state that a systematic review of the literature had been undertaken, and reported little detail about the search methods used. Consequently, it is impossible to determine whether the review was conducted in such a way as to identify all relevant research and minimise bias. The authors used a range of values from multiple studies to define triangular distributions around the model input parameters. This is not an appropriate way to characterise the uncertainty around such parameter estimates, as the use of a triangular distribution is not recommended and this method fails to account for study heterogeneity and differences in sample size. The authors did not consider the impact of differences between the primary studies on their estimate of effectiveness.

Validity of estimate of measure of benefit
The estimation of health benefits was modelled using a decision analytic model structure. The model used was appropriate for the study question. However, the interpretation of the values used to calculate lost productivity was not clear. In addition, although the analysis considered a lifetime horizon, only some monetary benefits appear to have been discounted, and the rate applied was not reported.

Validity of estimate of costs
The authors included all the categories of cost relevant to the perspective adopted. The costs of side effects from treatment were omitted from the analysis, as the authors considered that they would be small in relation to the costs of pandemic illnesses and death. This led to the costs of treatment or prophylaxis being underestimated. The costs and the quantities were reported separately, thus allowing an assessment of the generalisability of the study results. The resource use estimates were derived from published studies. Uncertainty around resource use was characterised using triangular distributions, with the minimum and maximum values determined by the literature. This is an inappropriate way to characterise uncertainty in a decision analytic model, as resource use data will not follow a triangular distribution. The prices and unit costs were taken from the authors’ setting and may incorporate charge data. A statistical analysis of the prices was not performed. Appropriate currency conversions were performed, and all costs were updated to the price year 2004 using the Consumer Price Index. However, the authors discounted indirect costs to
their net present value, although the rate applied was not reported.

Other issues
The authors made appropriate comparisons of their findings with those from other studies in different settings. The issue of generalisability to other settings with a similar tropical climate was addressed. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors reported that a further limitation of the study might be its disregard for quality of life. They also acknowledged that the model assumed that treatment and prophylaxis will not affect the transmission dynamics of the pandemic, and that the correlation between attack rates and pandemic duration was not incorporated.

Implications of the study
The authors suggested that policymakers should determine a plan of action for pandemic planning, particularly in light of the potential crossover of Avian flu.

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