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Predicting the influenza A (H1N1-2009) epidemic in Singapore using influenza-like-illness monitoring

Introduction

The novel strain of influenza A (H1N1-2009) that emerged in North America in early 2009 went on to cause the first influenza pandemic of the 21st century. Although the virus transpired to be much milder than in some previous pandemics, such as the 1918 or-to a lesser extent-the 1957 outbreaks,[1] it was able to spread rapidly across the globe, in part due to the coupling of the rapid growth of international travel since the last influenza pandemic in 1968 and the limited effectiveness of border screenings.[2] Many of the control measures deployed were costly or inconveniencing, such as daily temperature taking in schools or the incarceration of contacts of confirmed cases,[3,4] and as such it was desirable to sustain these only as long as necessary to minimise the impact, but no longer. To be able to plan how long to maintain control measures required some indication of how long the epidemic was likely to persist, but, due to the varied characteristics of pandemic influenza strains and the differences in influenza seasonalities in temperate as compared to tropical areas,[5] it was not clear to what extent the pattern of spread observed in past pandemics in Singapore or the (then) current pandemic in other countries could be extrapolated to guide expectations of how the epidemic would unfold in Singapore last year.

To be able to form reasonable short-term predictions, whether quantitative or otherwise, requires up-to-date, informative data. The current and long-standing approach to monitoring acute respiratory infections (ARIs) in Singapore is the weekly submission of cases presenting at the polyclinics, with automatic capture of clinical diagnoses.

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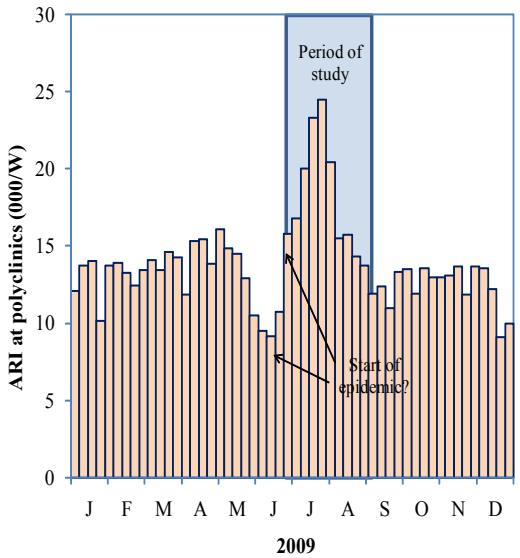
The polyclinics serve a little less than 20% of the population, so, although the age and socio-economic breakdown of their patients may be biased, these records provide a comprehensive indicator of the national burden of infections of the upper respiratory tract at a weekly time scale. There are various ætiological agents causing ARIs, such as rhinoviruses, influenza, parainfluenza and respiratory syncitial viruses,[6] and so this indicator is responsive to many kinds of outbreaks. However, this generality lessens its usefulness in tracking any particular pathogen, as ARI activity at any moment would be the cumulation of potentially many different epidemics, interacting with the considerable fluctuations due to environmental and social factors, such as school holidays, that can act together to mask the magnitude of the pathogen of interest, here, influenza (*Fig. 1*). The classical diagnosis for influenza is a short-lasting febrile illness with other symptoms of an ARI,[7] and although many cases who test positive for influenza on reverse-transcriptase polymerase chain reaction (RT-PCR) do not subsequently present a fever,[8] the fact that few (adult) patients with non-influenza infections develop a fever makes the diagnosis of influenza-like-illness (ILI, i.e. a febrile ARI) a clearer indicator of epidemic influenza activity than ARI alone.

Figure 1
Weekly acute respiratory infections in government polyclinics, 2009 (extracted from MOH, Weekly Infectious Disease Bulletin, volume 7). Although there is a pronounced peak corresponding to the influenza A (H1N1-2009) outbreak, the start and end of the outbreak is masked by stochasticity, presumably caused by school holidays, environmental factors, and outbreaks of other diseases of the upper respiratory tract.



In the weeks leading up to the beginning of sustained, unlinked community transmission, we therefore set up a general practitioner family doctor (GPFD) sentinel surveillance system to monitor ILI cases in near real-time. This we coupled to a mathematical model of a novel epidemic strain, fit daily to the data using a statistical procedure called particle filltering; we then used the fittted model and observed data to predict how the epidemic would evolve over the coming weeks. What follows is a brief overview of the methodology used and some of the results: for more details, see Ong et al[9]. We conclude with a discussion of how this approach might be adapted to routine monitoring of ILI counts from the computerised polyclinic medical records system.

Methods

We sent out invitations to over 500 GPFD clinics via email addresses obtained from the College of Family Physicians and the directory of pandemic preparedness clinics. Of these, 23 agreed to provide a line listing for each patient that presented with an ARI, detailing temperature at presentation along with various demographic information. These were to be submitted at the end of each working day or at the start of the next, by email or facsimile, to the study co-ordinator at Tan Tock Seng Hospital. He then processed these and uploaded a summary to a web

page that would then be accessed by a routine running on the web server of the Department of Statistics and Applied Probability at NUS (see below). Not all GPFDs submitted reports daily, and in particular fewer submissions were received at the weekend for obvious reasons.

An automated script would download the number of new cases and submissions each afternoon. These would then be summarised as a figure, and used to inform a compartmental model of disease spread[10], which was refitted to the data each day and then iterated forward by several weeks to form predictions, which were uploaded automatically to a publicly available web page. Predictions were probabilistic, providing a range of possibilities weighted according to uncertainty in the process underlying the epidemic as well as in the epidemic's current state. The model and inferential routines used to derive the predictions are quite involved, but a brief summary is informative. The model makes several simplifying assumptions, including that everyone starts off susceptible to the novel strain (but see Hancock et al[11]), that the risk of infection is proportional to the number of people currently infected, that importations arise at a constant rate, that a time-varying proportion of cases present to a GPFD (including those not in the study), that misdiagnoses occur at a constant rate, and various other assumptions that can each be argued against but which allow the model to be tractable numerically. In particular, the reader should note that the model is structured, unlike, for instance, many standard time series models, and a consequence of this structure is that predictions will always be that the epidemic at some point dies out. A major complication is that the model is for the total number of cases, of which only a "shadow" is observed, namely the number of cases presenting at the sentinel clinics. This was overcome using a simulation based, though still statistically rigorous, approach called particle filtering[12], which has been frequently used in ecological applications[13] but rarely in public health[14]. It should be noted that this statistical/mathematical modelling approach does not require that the participating GPFDs constitute a random sample of the population of GPFDs active in Singapore, which transpired to be important due to the low overall response rate.

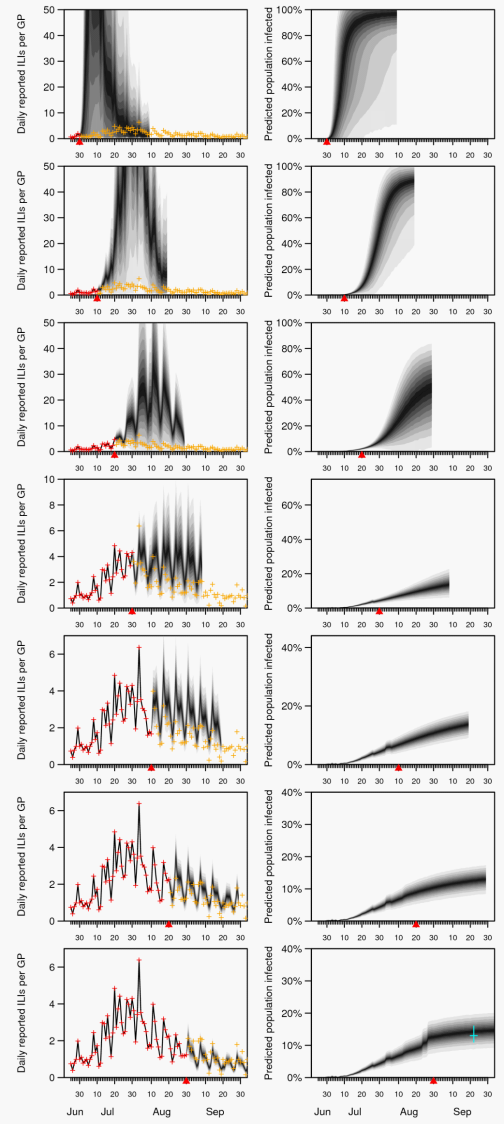
Results

Predictions of the future number of patients presenting at our GPFDs, as well as the cumulative, total number of cases in the population as a whole, are presented in *Fig 2*. Since there was little information at the early stages, initial predictions were hopelessly pessimistic. As more information was obtained, the predictions quickly honed in on what transpired to be the actual trajectory. The reader will observe that the pronounced day of the week effect, with more cases at the start of the week and fewer towards the weekend, is quite satisfactorily predicted by the model, and so there is no need to work with weekly summaries of cases, which in fact would obliterate much of the signal from such a rapidly invading pathogen with multiple infectious generations occurring within a one week window.

The eventual prediction of the total number of cases was somewhere between 10% and 20%. This concords very closely with an independent paired serological study performed by some other authors, which found around 13% of regular adult members of the community to have experienced a four-fold rise in blood titres over the period in question.[15] This could of course be merely fortuitous.

Figur 2

Evaluation of forecasts. (Left) Actual (red and orange crosses) and predicted (grey shaded area) average number of patients presenting with influenza-like illness per day at the average participating GPFD. The information used to form the forecast is indicated by the red crosses. The last day of information used in forming the forecast is indicated with a red triangle. Predictions here (and in the right-hand column) take the form of decreasing credible intervals, with the region spanned by the outermost polygons corresponding to 95% credibility. Orange crosses indicate future data not used in forming the forecasts. (Right) Predicted total number of people who (i) are currently symptomatic, or (ii) have recovered, assuming no pre-existing immunity. The last day of information used in forming the forecasts is indicated with a red triangle. The cyan cross on the bottom panel indicates the age-adjusted estimate of adult seroconversion in the community from an independent study (maximum likelihood estimate and 95% confidence interval[15]). Figure taken from Ong et al[9].



Discussion

The predictive routine proved to be remarkably successful in forecasting the pandemic, with the timing of the peak predicted at worst to within a fortnight, and usually within a week, although the predicted magnitude of the peak was initially grossly overestimated. The approach was computationally simple enough to be rerun on a daily basis and this, combined with the near real-time data collection, allowed forecasts to be made and posited on the web automatically every afternoon, thus informing the participating GPFDs about how severe the epidemic was likely to become, as well as ourselves on the best timing of other studies. Since the information was made public, and promoted in the local press, the predictions could be used by any organisation or individual, and, in fact, the web page attracted visits from overseas as well as from Singaporean internet protocol addresses.

An obvious difficulty we faced was maintaining the sentinel network. The increased workload was non-negligible, and as participation was purely voluntary, this imposed a considerable overall burden on the participants. We therefore wound the network down in October. Other countries, too, have struggled to maintain sentinel networks without providing support, whether financial or in-kind.[16.]

A more practicable long-term approach would be to exploit the existing system that the polyclinics and Ministry of Health (MOH) have in place, since scant additional work would be required from the polyclinics to marry their automated data collection with an adaptation of the modelling approach we used. During the local epidemic, the polyclinics were able to alter their data entry system to include an additional code for influenza-like illness, which enabled them to provide MOH with the weekly ILI consults pathway through the outbreak.[17] We have demonstrated that it is not diffcult to incorporate day of the week effects within an analysis, and believe that coarsening data to a weekly basis, while providing a useful description of long-term variations, in fact needlessly complicates statistical analysis. For the approach we used to be successfully used routinely to form real-time, probabilistic predictions of the risk of future epidemics, of both pandemic and non-pandemic influenza strains, would require:

- daily submission of ILI data from the polyclinics' systems to MOH; and
- adaptation of the model to incorporate the effect of genetic drift on the susceptible population.

We stress that once set-up, the approach can readily be automated. In addition, interpretation of such data can be enhanced when combined with data on the proportion of influenza-like illness consults testing positive for influenza on laboratory surveillance. A convenience sample of influenza-like illness patients presenting at our government polyclinics is routinely sampled in the existing laboratory surveillance programme, and tested by RT-PCR to determine the fraction of influenza-like illness which is attributable to influenza. Wedding these can thus give an informed estimate of the actual case load generated by influenza, and would reflect the fraction of influenza infections in the community which presents to polyclinics with an influenza-like illness. Work to evaluate such combined syndromic and laboratory approaches for influenza surveillance is ongoing.

(Reported by Cook AR[1], Lee HC[1], Ong JBS[2] and Chen MIC[2], Department of Statistics and Applied Probability, National University of Singapore[1] and Communicable Disease Centre, Tan Tock Seng Hospital[2])

Acknowledgments

This is an abridged and adapted version of a paper that has appeared in the Public Library of Science ONE[9] . For full details, the reader is directed to consult that paper. The project would simply not have been possible without the kind participation of 23 public-spirited GPFDs, to whom we are very grateful.

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Vaccination against pneumococcal disease

Pneumococcal disease

Streptococcus pneumoniae is a gram-positive encapsulated bacterium. Based on the differences in the composition of the polysaccharide capsule, about 90 serotypes have been identified. The capsule is an essential virulence factor.

Pneumococci are transmitted by direct contact with respiratory secretions from both infected ill persons and healthy carriers. Invasive pneumococcal disease (IPD), defined as a clinical condition in which *S. pneumoniae* is isolated from a normally sterile site, include pneumonia, meningitis, and bacteremia. The common non-invasive pneumococcal infections are otitis media, sinusitis and bronchitis.

Diseases caused by *S. pneumoniae* constitute a major public health problem globally in both children and adults. According to a 2002 WHO estimate, about 1.6 million cases of fatal pneumococcal disease occur worldwide annually, mostly in infants and the elderly[1]. In industrialised countries, the reported annual incidence of IPD ranges from 8 to 34 cases per 100,000 population, with the highest rates occurring in infants and children aged <2 years and in the elderly; in persons aged >65 years, the annual incidence ranges from 24 to 85 cases per 100,000 population[2]. Growing resistance of *S. pneumoniae* to essential antibiotics underlines the urgent need for vaccines to control pneumococcal diseases[3].

Morbidity and mortality in Singapore

In Singapore, the mean annual hospitalisation rate for IPD from 2000 to 2008 was 8.9 per 100,000 population (about 380 cases per year). This was similar to those of the United Kingdom, which had an annual incidence of 9 per 100,000 population. However, Singapore's rate was lower than that of the United States (20.7 per 100,000 population).

A total of 144 cases of IPD were notified from January to June 2009. The highest incidence rates were in children under 5 years of age and the elderly aged 65 years and above. Between 2000 and 2008, there were a total of 157 deaths from IPD, of whom 5 were under the age of 5 years. A study of IPD in children admitted to KK Women's and Children's Hospital from 1997 to 2004 showed that invasive pneumococcal disease had a complication rate of 25% and a mortality of 6% in Singapore[4].

In a national epidemiological study of pneumococcal disease among hospital patients, the investigators observed a downward trend in the annual hospitalisation rates from 2000 onwards, most notably among elderly aged ≥75 years and children aged <5 years. They postulated that this may partly be due to pneumococcal vaccination. However, they had no reliable data on vaccination coverage to substantiate this hypothesis[5].

Pneumococcal vaccines

23-valent vaccine

There are currently two 23-valent pneumococcal polysaccharide vaccines (PPSV23) available in Singapore: Pneumovax (Merck & Co.) and Pneumo 23 (Sanofi-Aventis), registered with the Health Sciences Authority of Singapore (HSA) in 1988 and

1998, respectively. Both vaccines include 23 purified capsular polysaccharide antigens of *S. pneumoniae* (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) and contain no adjuvant. These serotypes accounted for most cases (85-90%) of IPD in the United States and a few other industrialised countries before the introduction of routine childhood immunisation with PCV7. For primary immunisation, PPSV23 is administered as a single dose, by either intramuscular or subcutaneous injection.

7-valent vaccine

The 7-valent pneumococcal conjugate vaccine (PCV7) (marketed as Prevenar by Pfizer) is currently the only commercially available pneumococcal conjugate vaccine in Singapore and is licensed in more than 70 countries. It covers *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. It was registered with the HSA in May 2002. The target population groups are infants and children aged 6 weeks to 9 years.

Other vaccines

A 10-valent pneumococcal conjugate vaccine was recently approved for use in children by the European Medicines Agency (EMEA) in January 2009. The new vaccine, called Synflorix, is manufactured by GlaxoSmithKline and it offers coverage against three additional pneumococcal strains (serotypes 1, 5 and 7F) in addition to the seven serotypes included in Prevenar. The vaccine uses a novel protein carrier that may also confer protection against non-typable *Haemophilus influenzae* (NTHi). It has also been licensed in Australia and Canada.

A 13-valent pneumococcal conjugate vaccine for use in children, manufactured by Pfizer was approved for use by EMEA, Health Canada and most recently by the US Food and Drug Administration (FDA). This vaccine includes six additional serotypes (1, 3, 5, 6A, 7F and 19A) in addition to the seven serotypes included in Prevenar.

Childhood immunisation with PCV7

United States

In October 2000, the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC) recommended that PCV7 be used for all children aged 2-23 months and for children aged 24-59 months who are at increased risk for pneumococcal disease. In April 2008, the ACIP updated the recommendation for all healthy children aged 24-59 months who have not completed any recommended schedule for PCV7, to be administered with one dose of PCV7.

The ACIP recommends that all children aged below 5 years be vaccinated with PCV7. Infants should receive a primary series of 3 doses at 2, 4 and 6 months, followed by a fourth (booster) dose at age 12–15 months. For children 7-23 months of age, the primary series consists of 2 doses, given 2 months apart. A booster dose is recommended for children aged 7-11 months. For children aged 24-59 months, one dose is recommended for the primary series[6].

To enable children below 5 years of age to be up-to date with the new schedule, ACIP recommends that children who have yet to receive or complete the full vaccination series to be vaccinated with PCV7 appropriate for the respective age group.

United Kingdom

The UK's Department of Health (DH) recommends PCV7 for infants from 2 months of age as

part of the routine childhood immunisation schedule. The primary series consists of 2 doses given at 2 and 4 months. Although the currently available PCV7 is licensed for use as a three-dose primary series in infancy, evidence from immunogenicity studies in the UK showed that a two-dose primary immunisation course provides the same level of protection. A booster dose is recommended at 13 months of age for children who have received a complete course of two PCV7. For children from one year to under two years of age, the primary series consist of a single dose, with no reinforcing dose[7].

Australia

Australia's Department of Health and Ageing (DoHA) recommends PCV7 in the national immunisation programme for all infants from 2 months of age with a catch-up for children up to 2 years of age. The primary series of 3 doses is administered at 2, 4 and 6 months of age. Unless there is an increased risk of IPD, the additional benefits are not considered sufficient to justify a routine (fourth) booster dose. This recommendation is based on data from the pivotal randomised controlled trial suggesting similar efficacy against type-specific IPD with either 3 or 4 doses. For children aged 7-17 months, the primary series consists of 2 doses and for children aged 18-23 months, one dose is recommended[8].

Cost-effective analysis of pneumococcal vaccination among children in Singapore.

In view of the high cost of the vaccine, MOH's Health Services Research & Evaluation Division collaborated with Brandeis University, USA, to model the cost-effectiveness of pneumococcal vaccination for children in Singapore. The study was completed in October 2008.

In Singapore, basing the analysis on the birth cohort of 36,100 healthy infants in year 2007, vaccine and administration would cost $15.7 million and would save $2.5 million in medical costs in the vaccinated population annually. The vaccine would directly avert an expected 5.8 deaths and prevent 815 hospitalizations for meningitis, bacteremia, pneumonia, and otitis media in the vaccinated group of <5 years olds over the 5-year time horizon. When herd effects are considered, another 546 deaths and 1,956 hospitalisations are averted. Further, an additional $6.8 million in medical costs would be saved annually. Consequently, the incremental costs of vaccination versus no vaccination are $6.4 million annually (= $15.7 million – $2.5 million – $6.8 million).

Based on the World Health Organization's suggested standard comparison for cost-effectiveness, cost-effectiveness ratios in Singapore below $53,000 (Singapore's per capita GDP) are very cost-effective, while interventions costing more than $159,000 (three times the per capita GDP) are not cost-effective. Applying those thresholds to our findings indicates that:

a. The PCV7 can be considered a very cost-effective intervention in Singapore; even if a low herd immunity protection or considerable serotype replacements are assumed.

b. If no herd immunity is considered, the PCV7 vaccination cannot be considered cost-effective

Incorporation of pneumococcal vaccination into the national childhood immunisation programme

The Expert Committee on Immunisation (ECI), MOH, has recommended that pneumococcal

conjugate vaccine (PCV) be included in the national childhood immunisation programme (NCIP) based on the following considerations:

a. pneumococcal disease causes significant morbidity and mortality in Singapore

b. PCV is a safe and effective vaccine.

c. childhood vaccination is cost-effective

MOH has accepted the ECI's recommendation and has included pneumococcal vaccination as the 10th vaccine in the NCIP.

The 7-valent PCV is currently the only commercially available pneumococcal conjugate vaccine licensed in Singapore for use in children. The target population groups are infants and children aged 6 weeks to 5 years.

For routine immunisation, the ECI has recommended a schedule of 2 doses for the primary series and 1 booster dose (2 + 1 schedule). The 2 doses in the primary series are to be given at age 3 and 5 months, respectively and the booster dose at age 12 to 24 months (*Table 1*).

PCV can be concurrently administered with other childhood vaccines in the NCIP, but in a separate syringe at a separate injection site[6].

For catch-up immunisation schedule, MOH recommends catch-up immunisation for all children

Table 1
National childhood immunisation programme

Age	Vaccinations
At birth	BCG, Hepatitis B (dose 1)
1 month	Hepatitis B (dose 2)
3 months	DPT (dose 1), Polio (dose 1) PCV (dose 1)
4 months	DPT (dose 2), Polio (dose 2)
5 months	DPT (dose 3), Polio (dose 3) PCV (dose 2)
5 - 6 months	Hepatitis B (dose 3)
1 – 2 years	MMR (dose 1), PCV (booster)
18 months	DPT (booster 1), Polio (booster 1)
6 – 7 years (Primary 1)	MMR (dose 2), Polio (booster 2)
10 – 11 years (Primary 5)	DPT / DT (booster 2), Polio (booster 3)

DPT - diphtheria, pertussis, tetanus

MMR - measles, mumps, rubella

PCV - pneumococcal conjugate vaccine

under 5 years of age, as the rates of IPD is highest in this age-group, after the elderly.

For children below 12 months of age, 2 doses for the primary series and 1 booster dose should be given. The recommended interval between the first and second dose is eight weeks, with a minimum interval of four weeks. The minimum interval between the second dose of the primary series and the booster dose is eight weeks.

Children between 12 and 59 months of age who have asplenia or splenic dysfunction, or who are immunocompromised and may have a sub-optimal response to the first dose of vaccine, should receive 2 doses of PCV, with an interval of 2 months between doses.

For all other children between 12 and 59 months of age, a single dose of PCV is to be administered.

Payment

Three doses of the vaccine will be needed within the first 2 years of birth for the routine immunisation schedule. Parents can get their newborns immunised at their GPs, polyclinics or paediatricians.

With effect from 1 Nov 2009, Medisave use will be allowed for pneumococcal vaccinations in children under 5 years of age.

As per current practice, parents can also pay for the immunisation using their child's Baby Bonus cash gift and/or savings in his/her Child Development Account (CDA) at Baby Bonus-approved healthcare institutions. The Baby Bonus and CDA can also be used to pay for siblings' vaccinations.

Routine use of PPSV 23

United States

The ACIP recommends that the vaccine be administered to all immunocompetent persons in the following category:

i) Persons aged ≥65 years;

ii) Persons aged 2 – 64 years with chronic cardiovascular disease (including congestive heart failure and cardiomyopathies), chronic pulmonary disease (including chronic obstructive pulmonary disease and emphysema), or diabetes mellitus;

iii) Persons aged 2 – 64 years with alcoholism, chronic liver disease (including cirrhosis), or cerebrospinal fluid leaks;

iv) Persons aged 2 – 64 years with functional or anatomic asplenia (including sickle cell disease and splenectomy); and

v) Persons aged 2 – 64 years living in special environments or social settings (including Alaskan Natives and certain American Indian populations)[6].

In addition, immunocompromised persons aged ≥2 years who are at high risk of infection are also recommended to be vaccinated. Persons in this category includes those with HIV infection, leukemia, lymphoma, Hodgkins disease, multiple myeloma, generalised malignancy, chronic renal failure, or nephritic syndrome; those receiving immunosuppressive chemotherapy (including corticosteroids); and those who have received an organ or bone marrow transplant.

The strength of evidence supporting the recommendations for vaccination was the highest in persons

aged ≥65 years; persons aged 2 – 64 years with chronic cardiovascular disease, chronic pulmonary disease, or diabetes mellitus; and persons aged 2 – 64 years with functional or anatomic asplenia. This was followed by persons aged 2 – 64 years with alcoholism, chronic liver disease, or cerebrospinal fluid leaks (moderate evidence). Persons who are immunocompromised and those aged 2 – 64 years living in special environments or social settings had the least strength of evidence.

United Kingdom

The UK's DH recommends a single dose of PPSV23 to be administered to adults aged ≥65 years and persons aged ≥2 years who are in clinical risk groups (either as a booster dose following PCV7 or as a primary dose depending on age). The clinical risk groups include the following:

i) Asplenia or dysfunction of the spleen (including homozygous sickle cell disease and coeliac syndrome that may lead to splenic dysfunction);

ii) Chronic respiratory disease [including chronic obstructive pulmonary disease (COPD), chronic bronchitis and emphysema; and such conditions as bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD). Children with respiratory conditions caused by aspiration, or a neuromuscular disease (e.g. cerebral palsy) with a risk of aspiration];

iii) Chronic heart disease (including those requiring regular medication and/or follow-up for ischaemic heart disease, congenital heart disease, hypertension with cardiac complications, and chronic heart failure);

iv) Chronic renal disease (including nephrotic syndrome, chronic renal failure and renal transplantation);

v) Chronic liver disease (including cirrhosis, biliary atresia and chronic hepatitis);

vi) Diabetes (diabetes mellitus requiring insulin or oral hypoglycaemic Drugs);

vii) Immunosuppression [Due to disease or treatment, including asplenia or splenic dysfunction and HIV infection at all stages. Patients undergoing chemotherapy leading to immunosuppression. Individuals on or likely to be on systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day (any age), or for children under 20kg, a dose of 1mg or more per kg per day];

viii) Individuals with cochlear implants; and

ix) Individuals with cerebrospinal fluid leaks (including leakage of cerebrospinal fluid such as following trauma or major skull surgery)[7].

Australia

Australia's DoHA recommends PPSV23 in the national immunisation programme for persons in the following category:

i) All people aged ≥65 years;

ii) Aboriginal and Torres Strait Islander people ≥50 years of age and those 15–49 years of age who have underlying conditions placing them at risk of IPD;

iii) People aged ≥10 years who have underlying chronic illnesses predisposing them to IPD including:

a) asplenia either functional (including sickle-cell disease) or anatomical; where

possible, the vaccine should be given at least 14 days before splenectomy;

b) conditions associated with increased risk of IPD due to impaired immunity, eg. HIV infection before the development of AIDS, acute nephrotic syndrome, multiple myeloma, lymphoma, Hodgkin's disease and organ transplantation;

c) chronic illness associated with increased risk of IPD including chronic cardiac, renal or pulmonary disease, diabetes, alcohol-related problems;

d) CSF leak; and

e) tobacco smokers[8].

Booster doses of PPSV23

The ACIP recommends single revaccination for persons aged ≥65 years if they received the vaccine ≥5 years previously and were aged <65 years at the time of primary vaccination. Revaccination is also indicated for persons with functional or anatomic asplenia and immunocompromised persons. Routine revaccination of immunocompetent persons in other categories is not recommended.

The UK DH recommends re-immunisation with PPSV23 every five years for individuals with no spleen, splenic dysfunction or chronic renal disease. Routine revaccination is not currently recommended.

Australia's DoHA recommends maximum of 3 doses (i.e. 2 revaccinations) of PPSV23 at the interval of five years, based on data concerning adverse events and effectiveness. Non-indigenous adults aged ≥65 years are recommended one dose of revaccination, whereas non-indigenous adults aged <65 years with underlying chronic medical condition or smoker and asplenic individuals are recommended to be revaccinated with two doses of PPSV23 at an interval of five years.

WHO'S position on PPSV23

According to WHO position paper on PPSV23 published in October 2008, the results of randomized controlled trials (RCTs) of efficacy and effectiveness of PPSV23 and meta-analysis of such trials reviewed are consistent with a protective effect against IPD and all-cause-pneumonia among healthy young adults as well as a lesser degree of protection against IPD in individuals aged >65 years. In addition, most observational studies suggest an effectiveness as high as 50–80% against IPD in healthy adults, and similar results have been reported in some high-risk populations. However, RCTs have failed to demonstrate efficacy against IPD or all-cause pneumonia in individuals with immunocompromising conditions, regardless of age. As for the revaccination, on the basis of the data on the duration of vaccine-induced protection, WHO suggests one single revaccination ≥5 years after a first vaccination.

Many industrialised countries recommend PPSV23 immunisation of their elderly and other high-risk groups. However, in resource-limited countries, evidence does not support routine immunisation of the elderly and high-risk groups with PPSV23. In such settings, WHO recommends placing higher priority to introducing and maintaining high coverage of infants with PCV7 to gain benefit from herd immunity in adult age groups.

Recommendations for use of PPSV23 in Singapore

In Singapore, pneumococcal disease causes significant burden among the elderly, both in terms of morbidity and mortality. The PPSV23 is considered

safe both in terms of severe immediate reactions and potential long-term adverse consequences. Although data on efficacy and effectiveness of PPSV23 varies, many industrialised countries have recommended PPSV23 immunisation of their elderly and other high-risk groups based on currently available data.

A single dose of PPSV23 should be administered to the elderly ≥ 65 years of age, and persons aged 2 – 64 years at high risk of developing severe pneumococcal disease (*Table 2*).

Children aged two to five years in high risk groups should receive a single dose of PPSV23, in addition to PCV7. The interval between doses of PPSV23 and PCV7 should be at least two months.

Booster doses of PPSV23 are not recommended routinely. However, booster doses are recommended every five years in individuals with no spleen, splenic dysfunction and chronic renal disease.

Medisave can be used to pay for the cost of PPSV23 in children under the age of 5 years for whom the vaccine is clinically indicated. Medisave cannot be used to pay for the cost of PPSV23 in persons aged 5 years and older.

Table 2

High-risk groups for whom pneumococcal vaccination is recommended[7] (using 23-valent pneumococcal polysaccharide vaccine)

- Persons aged ≥ 65 years
- Persons aged 2-64 years in the following high-risk groups:
  - Persons with chronic illnesses
    - ◊ Chronic respiratory disease[a]
    - ◊ Chronic heart disease[b]
    - ◊ Chronic renal disease[c]
    - ◊ Alcoholism and chronic liver disease[d]
    - ◊ Diabetes
  - Cochlear implants
  - Cerebrospinal fluid leaks
  - Persons who have anatomic or functional asplenia (including conditions such as homozygous sickle cell disease and coeliac syndrome that may lead to splenic dysfunction)
  - Immunocompromised patients[e]

[a] Including chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema; and such conditions as bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD). Children with respiratory conditions caused by aspiration, or a neuromuscular disease (e.g. cerebral palsy) with a risk of aspiration.

[b] Including those requiring regular medication and/or follow-up for ischaemic heart disease, congenital heart disease, hypertension with cardiac complications, and chronic heart failure

[c] Including nephrotic syndrome, chronic renal failure and renal transplantation

[d] Including biliary atresia, cirrhosis and chronic hepatitis

[e] Immunosuppression, due to disease or treatment, including HIV infection at all stages, asplenia or splenic dysfunction, patients undergoing chemotherapy leading to immunosuppression, individuals on or likely to be on systemic steroids for more than a month at a dose equivalent to prednisolone at ≥ 20mg per day (any age), or for children under 20kg, a dose of ≥1mg per kg per day.

(Reported by Kita Y, Subramony H, Cutter J and James L, Communicable Diseases Division, Ministry of Health)

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An outbreak of gastroenteritis associated with roast turkey

Notification

On 22 Dec 2009, the Ministry of Health (MOH) was notified of 71 people suffering from food poisoning after a Christmas party held in a hospital on 18 Dec 2009. The food was supplied by a licensed caterer.

Epidemiological investigations

Following verification of the outbreak via phone interview, field investigations were immediately carried out. Attendees of the party were identified and their personal particulars such as age, gender, and ethnicity were recorded. Signs and symptoms of those who were ill and the types of medical treatment sought were obtained. A retrospective cohort study was conducted using a standard questionnaire to determine the vehicle of transmission based on food items consumed by both the well and ill attendees of the party. During field investigations, food and environmental samples were taken from the catering premises and tested for enteropathogens (*Shigella, Campylobacter, Vibrio, Salmonella*) as well as hygiene indicators such as total plate count and coliform count. Implicated food handlers were screened for enteropathogens, rotavirus and norovirus.

A case was defined as a person who developed two or more of the following clinical features: diarrhoea, nausea, vomiting, abdominal cramps, fever,

and headache after attending the Christmas party on 18 Dec 2009.

We used SPSS version 17.0 for the statistical analysis of data. The relative risk (RR) and confidence intervals (CI) were determined. A p value of <0.05 was considered statistically significant.

Results

A total of 67 cases were identified from 182 attendees of the party, giving an attack rate of 36.8%. Cases were mostly Singaporean Chinese (56.7%) females (70.1%) aged between 25 and 34 years (56.1%). The predominant symptoms were diarrhoea (97.0%) and stomach cramps (88.1%) followed by nausea (29.9%), headache (17.9%) and vomiting (16.4%). One had bloody diarrhoea. The majority of the cases (61.2%) self-medicated and 38.8% sought outpatient treatment. None was hospitalised.

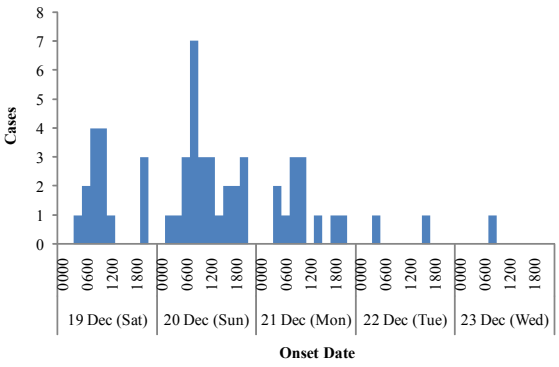
The onset of illness was from 0600 hours on 19 Dec 2009 to 0600 hours on 23 Dec 2009 with a single peak at 0800 hours on 20 Dec 2009 (*Fig. 3*). The mean and the median incubation periods were 40 hours (range 9 -109 hours).

A total of 128 (70.3%) of the 182 attendees responded to the questionnaire. Analyses of the food-specific relative risks based on 67 cases and 61 controls showed that consumption of roast turkey was significantly associated with illness. Those who ate this item were twice as likely to develop illness (RR 2.036; 95% CI 1.412 – 2.937) (*Table 3*).

No roast turkey samples were available for laboratory testing and none of the eight food samples taken at the catering premises were positive for enteropathogens. However, samples of green salad with dressing, honey-baked ham, vegetable medley and ice jelly were found to have high plate count (up to 580,000 colony forming units per gram) or total coliform count (up to 1,100 most probable number per gram) or both. One of the 10 implicated food handlers, who was asymptomatic, was tested positive for norovirus group II.

The implicated food served at the Christmas party was supplied by a meat wholesaler. The turkeys, imported from the USA were prepared under controlled hygienic conditions in the wholesaler's licensed premises as shown in *Fig. 4*. According to the wholesaler's recommendations, roast turkeys were to be delivered to the caterer within two hours after preparation and consumed within three hours of delivery or stored and reheated at 200 degrees Celsius before consumption. However according to the caterer, the cooked turkeys were delivered one day in advance on 17 December 2009 and stored in a refrigerator overnight and reheated at 160 degrees Celsius for 30 minutes the next day on 18 Dec 2009, after which the turkey was transferred to serving dishes for garnishing. Poor housekeeping and stacking of raw food was observed at the catering premises.

Figure 3
Onset chart of a food poisoning outbreak, Dec 2009



Comments

The clinical and epidemiological features of this outbreak (incubation period and food implicated) are consistent with salmonellosis. However the aetiology remained undetermined as no *Salmonella* organisms could be isolated from the stools or food remnants (both unavailable). The presence of norovirus in an asymptomatic food handler was an incidental finding.

A number of turkey-related food poisoning outbreaks have been reported in the USA. For example, undercooked turkey was responsible for an outbreak at a Thanksgiving dinner in Nevada, where raw turkey was cooked at 177 degrees Celsius for an hour without the use of a meat thermometer[1]. In another outbreak in Kentucky, undercooking of turkey resulted in proliferation of bacteria during the four-hour post-cooking period prior to consumption[2]. Reheating undercooked turkey and leaving it to stand for 10 hours unrefrigerated prior to serving, caused another outbreak in South Carolina[3].

A number of factors could have contributed to this outbreak. Improper storage of roast turkey delivered to the food catering premises, especially when kept at ambient tropical temperatures for prolonged period, could have led to further proliferation of bacteria which were not eliminated if the poultry was undercooked. Reheating turkeys lower than recommended temperatures would not be sufficient to kill the bacteria that might be present. Moreover, a lapse in personal and food hygiene and cross-contamination between raw and cooked food was noted during inspection. The findings of high coliform count and high total plate counts in some ready-to-serve foods in the catering premises further suggest a poor level of hygiene during the food preparation process.

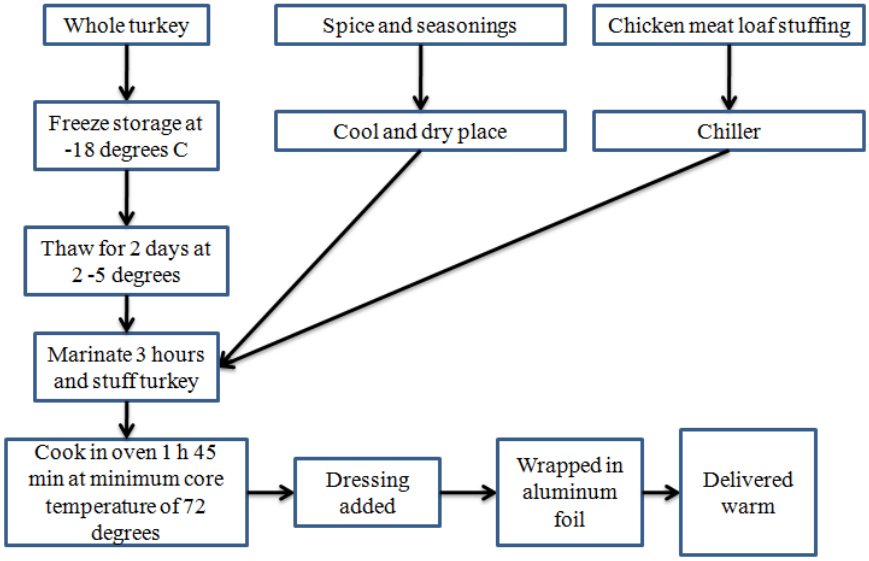
Table 3
Retrospective cohort study of 128 attendees of a food poisoning outbreak, Dec 2009

Exposure	Ill		Well		RR	P value	CI
	Exposed	Not exposed	Exposed	Not exposed			
Turkey*	44	23	18	43	2.036	<0.01	1.412 – 2.937
Green salad	19	48	23	38	0.811	0.291	0.533 – 1.188
Honey baked ham	40	27	35	26	1.047	0.790	0.746 – 1.469
Garlic rice	49	18	37	24	1.329	0.133	0.896 – 1.973
Sphaghetti	50	17	43	18	1.107	0.600	0.750 – 1.634
Grilled fish	60	7	52	9	1.224	0.462	0.684 – 2.191
Sauteed prawns	27	40	19	42	1.203	0.281	0.866 – 1.671
Shepherd's pie	44	23	36	25	1.329	0.437	0.648 – 2.722
Chipolata sausage	47	20	35	26	1.318	0.133	0.903 – 1.079
Vegetable medley	32	35	31	30	0.943	0.730	0.677 – 1.314
Log cake	26	41	26	35	0.927	0.661	0.658 – 1.305
Fruit cocktail	29	38	35	26	0.763	0.111	0.545 – 1.069
Pizza	10	57	7	54	1.146	0.566	0.740 – 1.773

* Statistically significant

Figure 4

Process flow of roast turkey from a meat wholesaler



(Reported by Tan BH, Lim SK, Toh HY, James L, Ooi PL, Communicable Diseases Division, Ministry of Health)

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An unusual outbreak of gastroenteritis in a primary school

On 4 Feb 2010, the principal of a primary school notified the Ministry of Health (MOH) of a group of primary 6 students who developed an acute onset of vomiting 15 minutes after attending a birthday party held in the school canteen on the same morning.

Epidemological investigations were immediately carried out to determine the cause, the extent of the outbreak and the mode of transmission. A site visit to the school revealed that the affected students were from the same class. A variety of titbits were brought from home by the person having the birthday and served at the party. There was also a science fair in the school premises where toys were sold. Students from the affected class had bought one particular 'Extrusion bean' toy, manufactured in Zhejiang, China at the fair.

Relevant clinical and epidemiological data were obtained. A retrospective cohort study was conducted to identify the risk factors contributing to the outbreak. Food samples were collected and sent for microbiological analyses. As the onset of symptoms was rapid, the samples were also tested for the presence of enterotoxins. All the canteen food handlers were referred to the Communicable Disease Centre, Tan Tock Seng Hospital, for screening of enteropathogens. As it was observed that toys purchased by the students exuded a fluid when squeezed, these toys were tested for a number of toxic chemicals, including phthalates.

Findings

A total of 13 primary 6 students (32.5%) out a class of 40 reported sick after attending the birthday party held from 0900 – 0930 hours on 4 February 2010. The symptoms were as follows: stomach ache (76.9%), nausea (69.2%), vomiting (46.2%), diarrhoea (38.5%) and headache (38.5%). Two had fever and one fainted. All cases received outpatient treatment and none from other classes were affected.

The majority of the students developed illness at 1000 hours. The incubation period ranged from 15 to 90 minutes (mean 20 minutes, median 40 minutes) (*Fig. 5*). Analyses of the risk factors based on 13 cases and 27 controls showed that students who had earlier played with an extrusion bean toy and had not properly washed their hands before consuming a variety of titbits was significantly associated with illness (RR: 5.56; 95% CI 1.812 – 17.031). These titbits included original potato chips (RR: 4.22; 95% CI 1.757 – 10.126), sour cream potato chips (RR: 4.02; 95% CI 1.808 – 8.934), mayo potato chips (RR: 2.50; 95% CI 1.118 – 5.593), barbeque potato chips (RR: 3.70; 95% CI 2.179 – 6.283), and cheese balls (RR: 4.00; 95% CI 2.272 – 7.043). Consumption of food items purchased from various food stalls in the canteen was not associated with illness (*Table 4*).

No enteropathogens, *Bacillus cereus* enterotoxins and *Staphylococcus aureus* enterotoxins were detected in all the 19 food samples which included different types of titbits, tested. Stools from two of the 19 asymptomatic food handlers were found to be positive for norovirus group II and *Aeromonas* species. Stool samples from 6 affected students were all negative for enteropathogens. Samples of fried eggs, grilled chicken, pineapple, and fishballs with crabstick obtained from canteen food stalls were found to have high plate counts (up to 1.8 x 10^7 colony-forming units per gam). No heavy metals (antimony, cadmium, copper, iron, tin, zinc) or pesticides (organochlorine, organophosporus, N-methyl carbamate, pyrethroids, dithiocarbamates) could be detected in any of the food samples. The 'extrusion bean' toy was found to contain three types of phthalates: dibutyl phthalates (DBP), diisobutyl phthalates (DIBP) and diethylhexyl phthalates (DEHP).

Comments

The clinical and the epidemiological features of this outbreak suggest the possibility of gastroenteritis

Figure 5
Onset of illness of an outbreak of gastroenteritis in a primary school, 4 Feb 2010

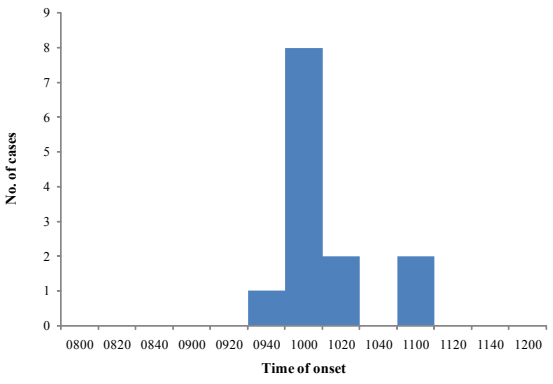

Table 4
Analyses of risk factors associated with an outbreak of gastroenteritis in a primary school, 4 Feb 2010

	Ill		Well		RR	p value	95% CI
	Exposed	Not exposed	Exposed	Not exposed			
Played with extrusion bean toy	11	2	15	12	2.962	0.071	0.761 – 11.531
Played with extrusion bean toy and ate titbits without washing hands*	10	3	5	22	5.556	0.001	1.812 – 17.031
Ate original potato chips*+	8	5	3	24	4.218	0.001	1.757 – 10.126
Ate sour cream potato chips*+	7	6	2	25	4.019	0.001	1.808 – 8.934
Ate mayo potato chips*+	5	8	3	24	2.500	0.043	1.118 – 5.593
Ate barbeque potato chips*+	3	10	0	27	3.700	0.009	2.179 – 6.283
Ate cheese balls*+	4	9	0	27	4.000	0.002	2.272 – 7.043
Ate prawn crackers+	1	12	3	24	0.750	0.736	0.129 – 4.356

* Significant + Students who also played with the extrusion bean toy and did not wash their hands before food consumption

caused by an enterotoxin or chemical in food. However, this could not be confirmed by laboratory tests and the symptoms were relatively mild. The presence of noroviruses and *Aeromonas* in two aymptomatic canteen food handlers is an accidental finding. The detection of phthalates in the 'extrusion bean' toy handled by the students could be the cause of the outbreak but also could be an incidental finding.

No quantification of the phthalates in the implicated toy was carried out. Blood and urine samples of the affected students were not available to test the presence of phthalate metabolites. The toy was small, around 6 cm in length, and the amount of chemicals that leaked to the surface would have been very small and thus the small quantity of phthalates ingested together with the titbits through contaminated hands might not be sufficient to cause serious acute gastrointestinal illness.

Phthalates are mainly used as plasticizers and are used, for example, to improve flexibility and durability in children's toys as well as in a large variety of consumer products. Diet is believed to be the main source of phthalates in the general population. DBP has been reported to cause vomiting, diarrhoea, nausea and stomach cramps when ingested[1]. Ingestion of 10g of DBP by a 23-year-old man led to nausea, vomiting and dizziness; and a few hours later, lacrimation, photophobia, pain in the eyes and corneal damage[2]. In another report, mild gastric disturbances with moderate diarrhoea occurred in two adults given 5 g or 10 g of DEHP. There were no other deleterious effects[3]. Both DBP and DEHP can lead to long term carcinogenic and toxic reproductive effects[4, 5]. The US EPA standards of chronic toxicity for DBP and DEHP are 0.8 and 0.02 mg/kg/day respectively[6].

Countries currently regulating phthalates include the European Union (EU), and the United States[7]. DBP and DEHP were banned from all toys and childcare items in the EU by the European Parliament in 2005 in view of their long-term toxic effects[8]. Toys are not regulated in Singapore.

Following this incident, as a safety precaution, a press statement was jointly issued by the Consumer Association of Singapore and MOH to alert all customers to the presence of toxic chemicals in the 'Extrusion bean' squeeze toy and those who owned the toys were advised to discard them immediately. Distributors and retailers of this product were also directed to recall and stop selling the toy.

(Reported by Tan BH, Lim SK, Toh HY, Cutter J, James L, Ooi PL, Communicable Diseases Division, Ministry of Health)

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