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Robert Moss, Alexander E Zarebski, Peter Dawson, Lucinda J Franklin,
Frances A Birrell and James M McCaw

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Communicable Diseases Intelligence is produced by:
Health Protection Policy Branch
Office of Health Protection
Australian Government
Department of Health
GPO Box 9848, (MDP 6)
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Anatomy of a seasonal influenza epidemic forecast

Robert Moss, Alexander E Zarebski, Peter Dawson, Lucinda J Franklin, Frances A Birrell
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Abstract

Bayesian methods have been used to predict the timing of infectious disease epidemics in various settings and for many infectious diseases, including seasonal influenza. But integrating these techniques into public health practice remains an ongoing challenge, and requires close collaboration between modellers, epidemiologists, and public health staff.

During the 2016 and 2017 Australian influenza seasons, weekly seasonal influenza forecasts were produced for cities in the three states with the largest populations: Victoria, New South Wales and Queensland. Forecast results were presented to Health Department disease surveillance units in these jurisdictions, who provided feedback about the plausibility and public health utility of these predictions.

In earlier studies we found that delays in reporting and processing of surveillance data substantially limited forecast performance, and that incorporating climatic effects on transmission improved forecast performance. In this study of the 2016 and 2017 seasons, we sought to refine the forecasting method to account for delays in receiving the data, and used meteorological data from past years to modulate the force of infection. We demonstrate how these refinements improved the forecast's predictive capacity, and use the 2017 influenza season to highlight challenges in accounting for population and clinician behaviour changes in response to a severe season.

Keywords: influenza; surveillance; forecasting; mathematical modelling; preparedness; response; research translation

Introduction

Methods for predicting the dynamics of infectious disease epidemics have received much attention since 2012¹, with particular focus on seasonal influenza epidemics in temperate climates.²⁻⁷ The United States Centers for Disease Control and Prevention (CDC) holds an annual influenza forecasting competition⁸ that attracts teams from around the world. The epidemic forecasting methods tested in these settings have the potential to support public health preparedness and response activities, although a number of practical challenges must be addressed if they are to be adopted and integrated into public health practice.^{3,9}

We have previously tailored epidemic forecasting methods to Australian data^{5,6} and have reported

on our pilot of a real-world application of these forecasts during the 2015 influenza season in Melbourne, Australia.⁹ In that study, we used influenza case notification counts to characterise influenza activity in one city whereby for each week of the season we generated forecasts of the weekly case notification counts for future weeks. A fundamental challenge encountered in that study was the delay in reporting and processing of case notifications, which arose due to an unprecedented number of notifications (relative to seasonal intensity¹⁰). Timeliness can also be affected by laboratory capacity when disease activity is high, and clinician testing behaviours also change over the course of the influenza season in response to disease activity in the community.

In this paper, we report on our forecasts for the 2016 and 2017 influenza seasons, in which we also collaborated with NSW and Queensland Departments of Health, to produce influenza forecasts for metropolitan Melbourne, Sydney, Brisbane, Gold Coast and Toowoomba. A key goal of this study was to account for delays in reporting and processing of case notifications, since relying on incomplete data introduces systematic biases into the forecasts and can both reduce the forecast accuracy and also increase the forecast uncertainty. We trialled a method for reducing these biases in the 2016 and 2017 forecasts.

We introduced 2 further refinements in our 2017 forecasts. The first was to use smoothed absolute humidity data from previous years to characterise climatic effects on influenza transmission; we have previously shown that this can improve the forecast predictive skill.⁷ The second was to base our initial expectations for the timing and size of the epidemic peak on the observed characteristics of previous seasonal influenza epidemics. These characteristics are influenced by many variables, including the circulating virus (sub)types, vaccine coverage, vaccine effectiveness and the number of specimens collected for testing.

Methods

Influenza notification data

The notifiable diseases dataset, from which we produce our forecasts, includes only those cases which meet the Communicable Diseases Network Australia (CDNA) case definition for laboratory-confirmed influenza.¹¹ These cases represent a small proportion of the actual cases in the community.¹² Some notifications did not include a symptom onset date, so we used the specimen collection date as a proxy. Using specimen collection date is considered not to distort the data substantially since we used weekly case counts, while symptomatic influenza infection (used here as a proxy for transmission potential) typically lasts several days¹³ and the majority of notifications arise from tests that identify the presence of virus (e.g. PCR) rather than the

presence of antibodies (i.e. serology). We also mitigated the potential impact of events such as public holidays by generating forecasts on Thursdays for the week ending on the previous Sunday (i.e. 4 days later).

Separate influenza forecasts were produced for metropolitan Melbourne, Sydney, Brisbane, Gold Coast and Toowoomba. The state capitals (Melbourne, Sydney, Brisbane) are also the primary urban centres in these states, and are located at different latitudes on the east coast of Australia. Two other locations in proximity to Brisbane were also chosen so that comparisons could be made against the Brisbane forecasts: the Gold Coast (also located on the east coast, about 60 km south of Brisbane) and Toowoomba (inland, about 125 km west of Brisbane). Both are large regional population centres that historically experience significant seasonal influenza activity.

Forecasting methods

Forecasts were generated every Thursday from April to November 2016, and from April to November 2017, using weekly case notification counts up to the most recent week (ending on Sunday). We reported the median, 50% credible interval and 90% credible interval for the future predicted weekly notification counts and timing of the epidemic peak. Every week the lead modeller (R. Moss) emailed a summary and analysis of these outputs to participating public health staff in each jurisdiction, who were asked to provide feedback about their interpretation of the forecast predictions, the plausibility of these predictions, and what aspects of these forecasts were of particular utility for their public health activities.

As described in detail elsewhere^{5,6}, our forecast method combines an SEIR (susceptible-exposed-infectious-recovered) population model of infection with the weekly influenza case notification counts, through the use of a particle filter. The weekly influenza case notification counts were modelled using a negative binomial distribution with a fixed dispersion parameter k , and assum-

ing some constant “background” notification rate. The expected number of cases (above the background rate) was proportional to the weekly incidence of infection in the model, and this proportion was characterised by the observation probability p_{id} .

The observation probability represented the probability of an infected individual resulting in a notified case (i.e. the probability of seeking health care and having a specimen collected). Values for p_{id} and k were selected from retrospective forecasts using notifications data from previous seasons. The background notification rate was estimated using notification counts from March to May, inclusive, to reflect the disease activity observed in autumn (i.e. just prior to the season onset). This also avoids possible over-estimation by ignoring earlier months, where there may be continued importation of influenza cases during the northern-hemisphere influenza season. These parameters were selected separately for each of the forecast locations (Melbourne, Sydney, Brisbane, Gold Coast, Toowoomba), and are reported in Table S1.

Each week, before generating a forecast for each of the locations, we measured how many additional cases (Δ_i) had been reported for the *previous week* during the current week (i.e. since the previous forecast was generated). We then assumed that the number of cases reported for the current week (c_{i+1}) could increase by the same *amount*, and conditioned the model simulations on the likelihood of observing between c_{i+1} and $c_{i+1} + \Delta_i$ cases in the current week. To illustrate, consider the scenario where 200 cases are reported for week n when the forecast for week n is generated, and that one week later (a) this total has increased to 250 cases; and (b) there are 300 cases reported for week $n+1$. When we generate the forecast at the end of week $n+1$, we therefore assume that the total for week $n+1$ could be as high as $300 + (250-200)=350$ cases. We refer to these estimated case totals as “estimated upper bounds” in the remainder of this manuscript.

Prior to 2017, the SEIR model parameters were independently sampled from broad, uniform

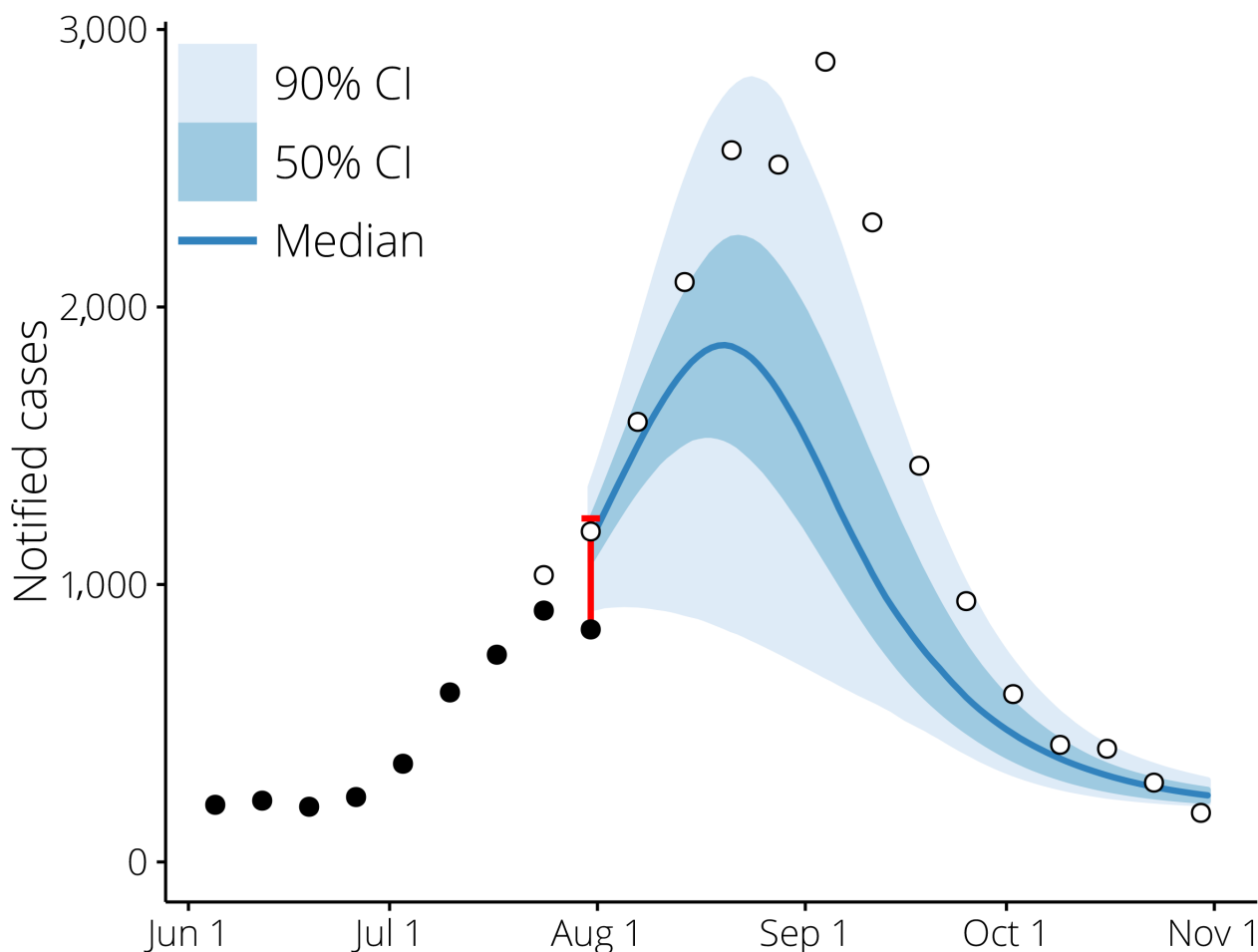
distributions (see Table S2). This meant that the forecast predictions initially considered a much wider range of epidemics (in terms of timing, duration, and magnitude) than have been observed. In 2017, we modified this sampling process to better reflect the characteristics of previous influenza seasons. This means that before an epidemic signal is present in the notifications data, the forecasts predict outbreaks of similar timing, duration, and magnitude, as observed in past epidemics. This was achieved by (a) constructing a multivariate normal distribution for the peak timing and size in previous years; (b) sampling parameter values from the uniform distributions; (c) simulating the epidemic that these parameter values describe; and (d) accepting each sample in proportion to the simulated epidemic’s probability density. Identification of the circulating influenza (sub) types very early in the influenza season could be used to further refine this prior, by constructing it from past epidemics in which similar (sub) types were circulating.

In 2017, we also introduced the concept of “seasonal forcing” into the model, to account for the influence that climate has on the force of infection. This seasonality was characterised by smoothed absolute humidity data for each city in previous years, using time-series data from a single weather station in each city, and we have previously shown that this can improve the forecasts’ predictive skill⁷ (see the supplementary material for details¹⁴). Note that there are many other factors that influence the overall shape of the case notifications data, and forecast performance is highest when humidity exerts only a modest effect on transmission in the simulation model. Humidity is not responsible for initiating epidemic activity in the model. Indeed, it is unknown to what extent climatic factors such as humidity *directly* contribute to transmission in temperate climates, versus human behavioural changes in colder conditions.

Results

Figure 1 shows the Sydney influenza forecast for the week ending 31 July 2016, which was

Figure 1: Example of an influenza forecast: Sydney, 31 July 2016. The weekly number of notified laboratory-confirmed influenza cases *at the time of the forecast* are shown as black points; hollow points show the case numbers as reported *at the end of the season*. There were 838 cases for the week ending 31 July when this forecast was generated, and our estimated upper bound was 1,238 cases. This forecast was therefore conditioned on the likelihood of observing between 838 and 1,238 cases, as indicated by the vertical red line. The forecast comprises a median prediction (blue line) and credible intervals (shaded blue regions) indicate the forecast uncertainty.



generated on 4 August 2016. The number of case notifications for each of the preceding weeks *at the time of forecasting* are shown as black points, while hollow points show the totals for every week *as reported by the end of the season*. Note that the weekly totals for the weeks ending 24 July and 31 July increased *after* this forecast was generated. At the time of forecasting 838 cases were reported for the week ending 31 July; we estimated an upper bound of 1,238 cases (as indicated by the red line) and the final total was 1,191 cases (indicated by the hollow point). The forecast prediction comprises a median prediction (blue line) and credible intervals

(shaded blue regions) that indicate the forecast uncertainty. In a perfect forecast, the future case counts would be distributed evenly above and below the median prediction, about half of these counts would fall within the 50% credible interval, and about 90% of these counts would fall within the 90% credible interval. In this example, the epidemic peak is predicted to occur about 2 weeks earlier than the true peak, and the median prediction under-estimates most of the future case counts. Note that the peak timing predictions are also presented as separate plots, and will be shown in subsequent figures in this manuscript.

Figure 2: The change in weekly case counts, from the initially-reported values (grey horizontal lines) to the final values as reported at the end of the season (grey hollow points), and the estimated upper bounds (black stars) given the initially-reported counts. Results are shown for each of the forecast locations in the 2016 and 2017 influenza seasons.

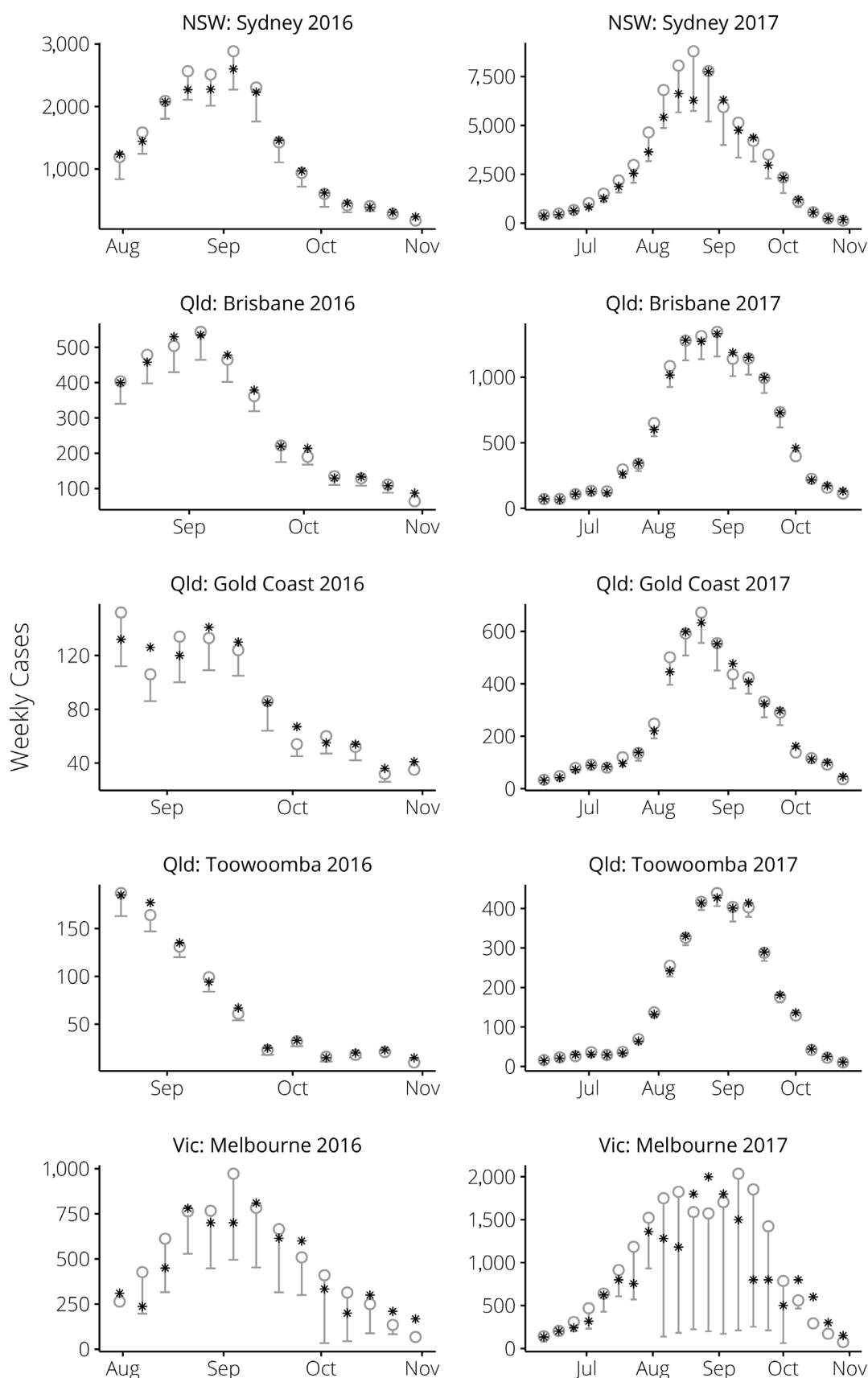


Figure 2 shows how the number of cases reported for each week continued to increase in subsequent weeks: each grey bar depicts the interval between the initial count (i.e. at the time of forecasting) and the count reported at the end of the season. The estimated upper bounds are shown as black stars; perfect estimates would coincide with the top of each grey bar. With the exception of Melbourne, where there were longer delays in case notifications⁹, the upper bound estimates performed well and generally provided much more accurate estimates of the final case counts. The performance of these estimates are summarised in Table 1.

Table 1: A summary of the upper bound estimates, expressed as percentages of the final counts for each week: mean absolute error (MAE), standard deviation (SD), and the results of the 2-sample, 2-sided Kolmogorov-Smirnov test (KS test). This test was used to compare the residuals (a) prior to the epidemic peak, and (b) after the epidemic peak; significant differences ($P < 0.05$, shown in bold) were identified for: Sydney, Gold Coast and Toowoomba in 2017.

Setting	MAE	SD	KS test
NSW: Sydney 2016	7.9	11.5	0.165
NSW: Sydney 2017	13.0	14.8	0.002
Qld: Brisbane 2016	6.6	11.1	0.709
Qld: Brisbane 2017	5.3	7.5	0.065
Qld: Gold Coast 2016	10.9	12.4	-
Qld: Gold Coast 2017	8.0	10.8	0.03
Qld: Toowoomba 2016	10.5	15.1	-
Qld: Toowoomba 2017	5.7	7.5	0.013
Vic: Melbourne 2016	31.0	48.3	0.316
Vic: Melbourne 2017	34.4	46.1	0.054

The upper bound is estimated by adjusting the initially-reported value, based on the observed increase in case counts for prior weeks. However, disease incidence increases faster than linearly in the early stages of an epidemic, and decreases faster than linearly in the later stages of an epidemic. It is therefore reasonable to expect that the upper bound estimates will (a) systematically

underestimate the final counts for the weeks prior to the epidemic peak; and (b) systematically overestimate the final counts for the weeks after the epidemic peak. In order to detect this type of bias, we used the two-sample, two-sided Kolmogorov-Smirnov test to identify significant differences between the residuals prior to, and after, the observed peaks. Significant differences ($P < 0.05$) were only identified for Gold Coast, Sydney and Toowoomba in 2017. Note that there were insufficient data points to evaluate this test for the Gold Coast and Toowoomba epidemics in 2016, as delays in weekly case counts only became evident at the time of the epidemic peak.

The peak timing predictions for 2016 are shown in Figure 3, over the 15 weeks prior to the epidemic peaks. We used non-informative model priors in 2016, and so the early peak timing predictions in all cities were highly uncertain (i.e. very broad) and inaccurate. From 5–8 weeks prior to the epidemic peak, once the notifications data contained evidence of epidemic activity, the peak timing predictions became much more certain (i.e. narrow) and, with the exception of Melbourne where the weekly counts were subject to larger delayed increases (see Figure 2), much more accurate. In the 5 weeks prior to the epidemic peak, the peak timing predictions were accurate to within one week in the Queensland locations included in this study, and to within 2 weeks in Sydney.

The peak timing predictions for 2017 are shown in Figure 4, and reflect 2 key results. Firstly, the 2017 seasonal epidemics were so large (in terms of notified cases) that they lay *outside* of our model priors. That is, the observed epidemics were so large that they lay outside of the admitted possibilities in our original forecasts. This became evident in July and August, as epidemic activity continued to increase beyond all expectations (from both expert opinion and from historical data). We re-calibrated our forecasts to correct for this.

Accordingly, we used a higher observation probability $P_{id}^* = 4 \times P_{id}$, based upon expert opinion during our weekly forecast discussions and also

Figure 3: Week by week forecasts of the 2016 epidemic peak timing, plotted against the number of weeks prior to the actual peak at which the forecast was made. The timing is reported as ISO 8601 week numbers and the timing of the actual peaks are indicated by the horizontal dashed lines. The predictions are imprecise and inaccurate until the case notifications data contain evidence of a seasonal epidemic.

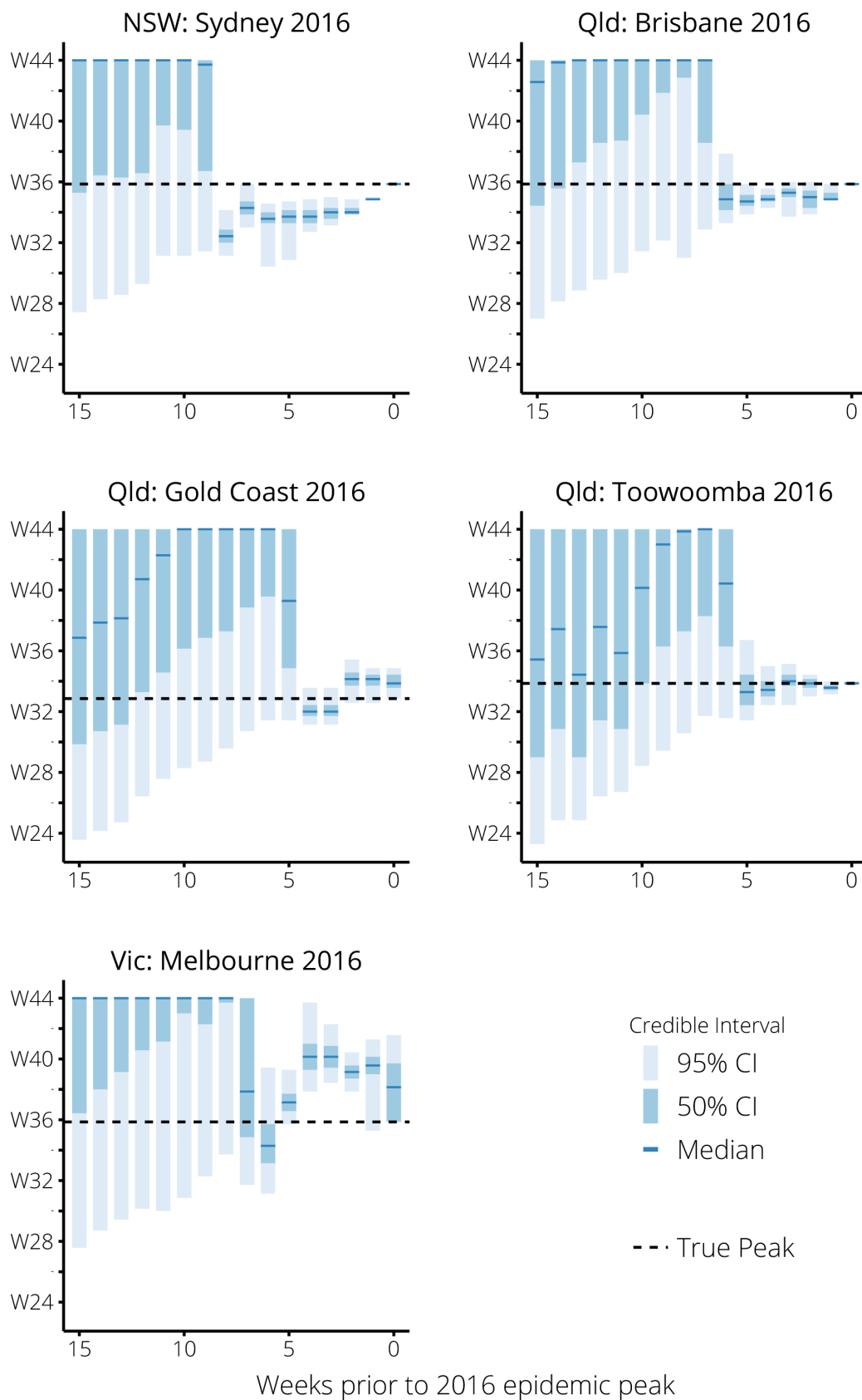
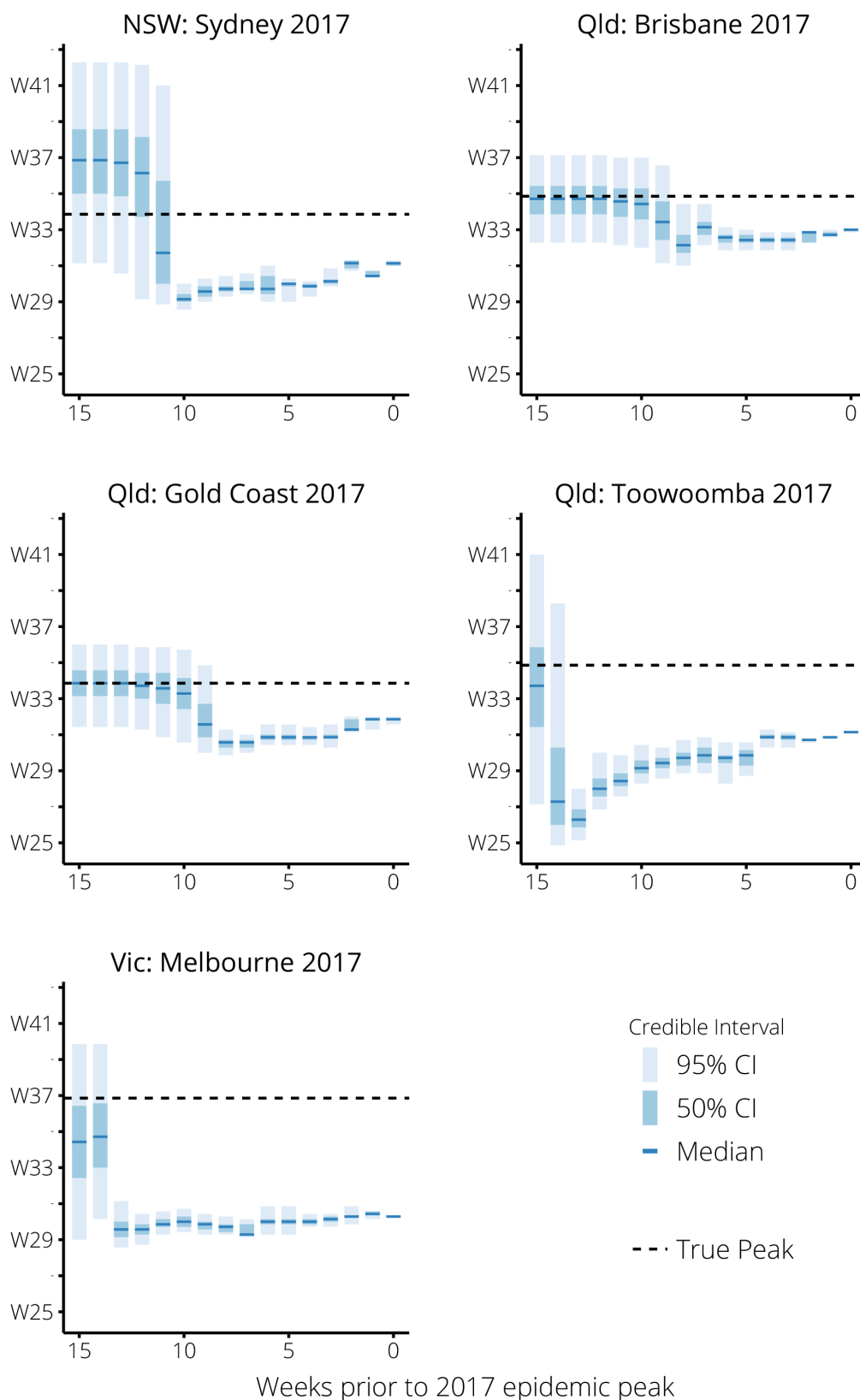


Figure 4: Week by week forecasts of the 2017 epidemic peak timing, plotted against the number of weeks prior to the actual peak at which the forecast was made. The timing is reported as ISO 8601 week numbers, and the timing of the actual peaks are indicated by the horizontal dashed lines. The predictions are reasonably precise and accurate prior to the seasonal epidemics, due to our use of informative priors. The predictions then become inaccurate due to the unprecedented scale of the 2017 influenza season.



informed by our experiences in our 2015 pilot study.⁹ Note that this was a coarse adjustment; there was no strong evidence to rule out a three-fold, five-fold, or other increase. It is important to note that this adjustment was not a simple re-scaling of the forecast predictions. The observation probability characterises the relationship between model infections and case notifications. Model infections occur by removing individuals from the susceptible population, and so a change in the observation probability affects how rapidly the susceptible population is depleted in the model. It is this depletion of the susceptible population that determines when the epidemic peaks and then begins to decrease. Therefore, a change in the observation probability affects the timing and duration of the predicted epidemic, as well as its size. The re-calibrated peak timing predictions for 2017 are shown in Figure 5, and are greatly improved when compared to the predictions obtained prior to this re-calibration (as shown in Figure 4). The Melbourne forecast performance was again affected by large increases in weekly case counts, relative to the initially-reported values (see Figure 2).

As indicated by the dashed vertical lines in Figure 5, this re-calibration was performed 2 weeks prior to the peaks in Sydney and the Gold Coast, 3 weeks prior to the peaks in Brisbane and Toowoomba and 5 weeks prior to the peak in Melbourne. In ideal circumstances, evidence of inappropriate model calibration would be identified and acted upon earlier than 2–3 weeks prior to the epidemic peak, so that the updated predictions would be of greater utility.

The second key result from our 2017 forecasts is the effect of the informative model priors, as shown in Figures 4 and 5. Prior to the evidence of epidemic activity, the peak timing predictions were much more certain (i.e. narrow) than at the corresponding period in 2016, and they were also *accurate*, because the 2017 seasonal epidemics peaked at a similar time to previous seasonal influenza epidemics. Had the forecasts been appropriately calibrated at the start of the season (e.g. by having prior knowledge that a

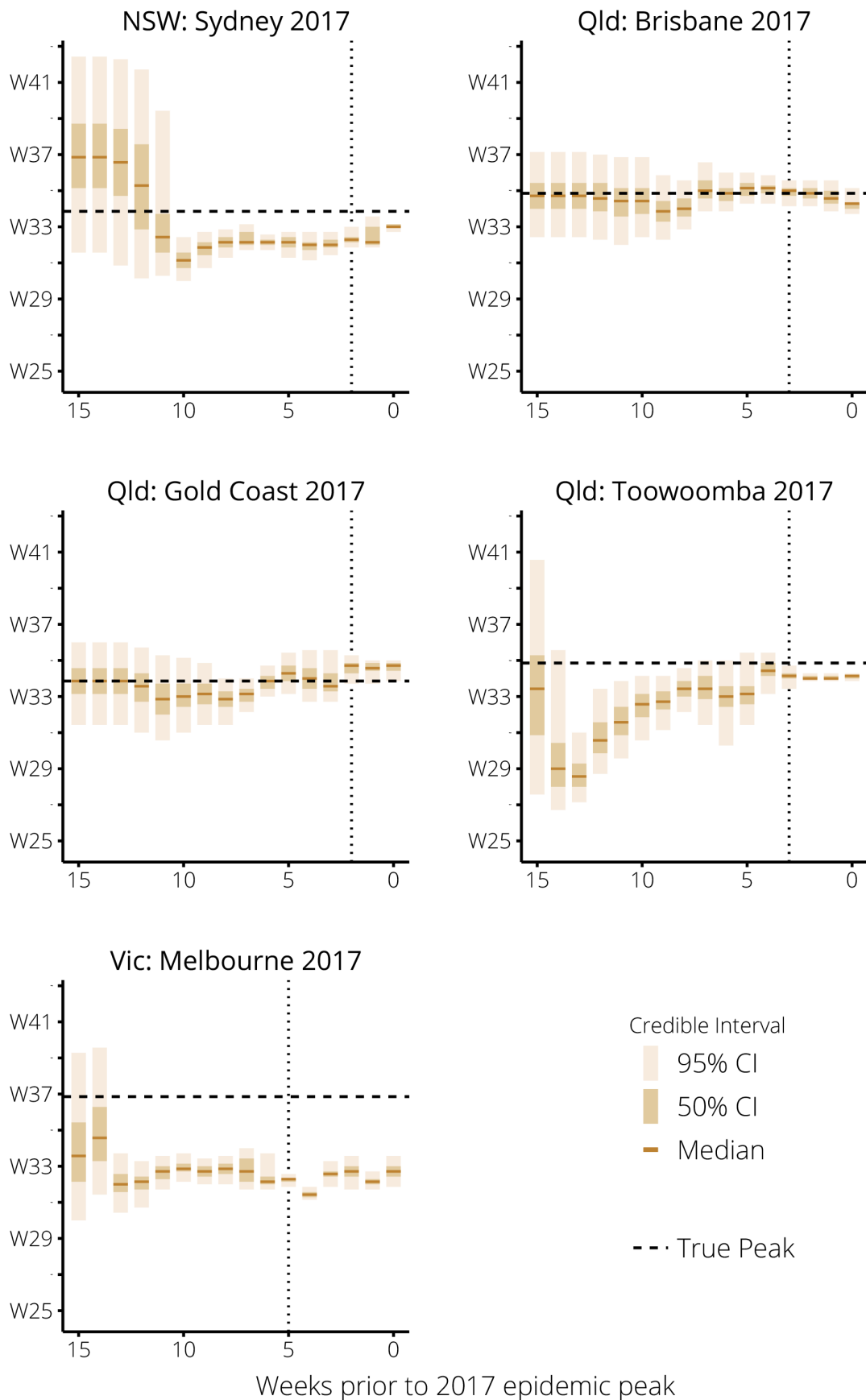
larger than normal epidemic might be expected) these priors would have substantially improved forecast performance.

In 2016, we obtained accurate peak size predictions for Brisbane and Gold Coast 2 weeks prior to the peak, and underestimated the peak size in Sydney, Toowoomba and Melbourne. In 2017, all forecasts underestimated the peak size. The size of the epidemic peak is intrinsically harder to predict than its timing, because the peak size is far more sensitive to the parameters; even a small change in R_0 or the observation probability can lead to a substantial change in the peak size. Based on previous forecasting studies, we would only expect to have good predictions of the peak size 2–3 weeks prior to the peak.^{5,6}

Discussion

The forecasting refinements that we introduced in 2016 and 2017 improved the forecast performance, and so we will continue to use them in future influenza seasons. We know that the number of cases reported for the most recent week is *always an underestimate* of the true value, and that unless this is accounted for, it introduces a negative bias into the forecasts. The method that we presented here to account for delays in case notifications data yielded reasonably accurate predictions of the weekly case totals, especially for delays of 1–2 weeks; its performance was reduced when longer delays were evident. With confidence in this method, in future influenza seasons we anticipate conditioning the forecasts on the likelihood of observing the estimated upper bounds themselves, rather than on the likelihood of observing *any value between* the currently-reported total and the estimated upper bounds (as was done in this study). This will avoid the negative bias associated with using the reported number of cases for the most recent week. These improved estimates of the weekly case totals are also extremely useful when re-calibrating the forecasts, because they allow greater confidence to be placed in the inferences drawn from the data. This is of particular relevance in seasons like 2017, where the epidemics that occurred in each city differed

Figure 5: Week by week forecasts of the 2017 epidemic peak timing, once the forecasts were re-calibrated. The timing of the actual peaks are indicated by the horizontal dashed lines, and the vertical dotted lines show when the re-calibrations were performed. The predictions are substantially improved as a result of the re-calibration (i.e. compared to Figure 4).



greatly from previous years' epidemics, and were beyond the scope of epidemics considered in our model priors. The additional refinements that were introduced in 2017 — seasonal modulation of transmission and the informative model priors — also improved forecast performance, although this cannot be quantified precisely due to the unprecedented scale of the 2017 influenza season in eastern Australia.

Indeed, the absence of denominator data for the case notifications is a fundamental challenge of using these data.¹⁵ It means that forecast accuracy can be very low when there is a substantial change in epidemic scale from one year to the next, because the relative contributions of increased disease activity, clinical severity of disease, and increased testing (and any change in vaccine effectiveness, for that matter) cannot be reliably distinguished, and these factors can combine to greatly increase the scale of the case notifications data (as appears to have occurred in 2017¹⁶). It is true that case notification denominators are available in some jurisdictions, but this was not the case for all of the locations considered in this study. For simplicity, we elected to use the same type of surveillance data in each setting. Incorporating percentage-positive data into this forecasting framework also bears careful consideration because, similar to the case notification counts used here, they are influenced by healthcare-seeking behaviours and testing practices.

This can be surmounted to some degree by admitting a wider range of epidemic sizes in the model prior, at the cost of increasing forecast uncertainty. It could also be mitigated by identifying the circulating strains (and adjusting the model to incorporate knowledge about the virulence of the predominant circulating strain, or accounting for the degree of evolutionary change¹⁷) in the early stages of the epidemic and adjusting the expected epidemic size in the model priors. We are currently exploring various avenues for identifying early signals of substantially larger (or smaller) seasons, including synthesising surveillance data across multiple levels of the surveillance pyramid¹², and using genetic

data obtained from specimens collected early in the season. The ability to define appropriate expectations, and to adjust them as new evidence become available, is an important methodological challenge for the global infectious disease forecasting community. Addressing this challenge requires both a better understanding of the biological drivers of transmission and new approaches to make best use of novel data streams.¹⁸

A simpler alternative, which capitalises on the use of an informative model prior, would be to assume that the timing of the seasonal peak will be consistent with the distribution of peak timing observed in previous seasonal influenza epidemics. As evidence of epidemic activity becomes apparent in the case notifications data, if the predicted peak timing in the forecasts begin to differ from this peak timing distribution, the forecasts could be re-calibrated so as to yield peak timing predictions that are consistent with this distribution. In 2017, this would have naturally increased the scale of the forecast epidemics, because the peak timing predictions differed greatly from the model priors (Figure 4). Such an approach for continual re-calibration of the case notifications data could be used to estimate the case notifications denominator, and could be validated in those jurisdictions where denominators are available.

Observations of the preceding northern-hemisphere influenza season could conceivably assist in calibrating the forecasts, under the assumption that the following southern-hemisphere influenza season would have similar characteristics. However, the relationship between the northern and southern hemispheres is highly variable and biologically complex.¹⁹ The experience of influenza across Australia is also highly variable. In particular, the northern regions are tropical/subtropical and experience endemic influenza activity with sporadic outbreaks, in contrast to the seasonal activity typical of temperate climates. Epidemic forecasting methods can be used in such settings to predict disease activity over shorter timescales (e.g. 1–3 weeks ahead²⁰). This would require modifications to

the infection model used in this study, such as changing how the background rate is estimated and how climatic factors influence transmission (about which there is much uncertainty²¹).

Reliable epidemic forecasts could support public health preparedness and response in several ways. For example, there is evidence that vaccine-acquired immunity can wane quickly enough that provision of seasonal influenza vaccine too early in the year might result in vaccinees having little, if any, protection when it is most needed.²² If the timing of the seasonal peak were known sufficiently far in advance, it could influence vaccination policies and help ensure that vaccine-acquired immunity is maintained while the risk of infection is high. There is also the issue of influenza virus co-circulation; recent years have seen co-circulation of influenza types A and B in Australia, with type A dominating early and type B dominating later in the season. Accurately modelling the co-circulation of multiple influenza viruses requires precise knowledge about, e.g. population susceptibility and cross-protective immunity.²³ However, since the co-circulation of influenza types A and B typically exhibits 2 distinct epidemic curves, an alternative is to model each subtype/lineage as circulating independently. Combining these forecasts with knowledge of relevant clinical factors (e.g. expected age distribution of severe cases) could then be used to predict measures of clinical burden such as influenza-related hospitalisations.

Conclusions

Ultimately, to improve our understanding of seasonal influenza burden we need to synthesise data from many levels of the disease surveillance pyramid^{24,25}, and this challenge is exacerbated when trying to develop this understanding for near-real-time and/or predictive purposes. These kinds of data are available in Australia, from healthcare-seeking behaviours reported in Flutracking weekly surveys¹² to sentinel general practice influenza-like illness (ILI) data¹⁰ and sentinel hospital influenza admissions data²⁶, but synthesising these disparate data sources

in a *meaningful* way is highly non-trivial.^{6,27,28} Challenges include differences in case specificity (e.g. syndromic diagnoses vs laboratory-confirmed influenza), reporting delays, and the sample populations (e.g. Flutracking participants, sentinel sites). Engagement with public health staff is also critical to improving forecast performance (e.g. by incorporating expert knowledge) and for ensuring the value of these forecasts as a tool for public health.^{29,30}

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Author affiliations

Robert Moss¹, Alexander E Zarebski², Peter Dawson³, Lucinda J Franklin⁴, Frances A Birrell⁵ and James M McCaw^{1,2,6}

1. Modelling and Simulation Unit, Melbourne School of Population and Global Health, The University of Melbourne, Victoria.
2. School of Mathematics and Statistics, The University of Melbourne, Victoria.

3. Defence Science and Technology Group, Victoria.
4. Communicable Diseases Section, Health Protection Branch, Regulation Health Protection and Emergency Management Division, Victorian Government Department of Health and Human Services, Victoria.
5. Epidemiology and Research Unit, Communicable Diseases Branch, Prevention Division, Department of Health, Queensland.
6. Murdoch Childrens Research Institute, Victoria.

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