PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Timeliness of signal detection for adverse events following influenza vaccination in young children: a simulation case study
AUTHORS	Jacoby, Peter; Glover, Catherine; Damon, Chloe; Fathima, Parveen; Pillsbury, Alexis; Durrheim, David; Gold, Michael S; Leeb, Alan; Snelling, Tom

VERSION 1 – REVIEW

REVIEWER	Patrick Zuber World Health Organization Geneva, Switzerland
REVIEW RETURNED	04-Jun-2019

GENERAL COMMENTS	This article proposes a simulation, within a novel active surveillance system AusVaxSafety that uses an electronic data system, SmartVax, that automatically sends SMS to vaccine recipients. This system solicits reports of adverse events following immunization during the days that follow vaccine administration. In particular the occurrence of fever and medical visits are documented. The simulation exercise evaluated the sensitivity and timeliness of active surveillance, using estimates of data which would be have been available if this system had been in place in 2010. That year, the Fluvax from CSL Biotherapies led to an unusual number of febrile seizures. The paediatric influenza vaccination program that had been officially launched on 19 March was suspended on 22 April based on a spike in fever events following vaccination that got notified to the Western Australia health authorities on 13 April. The weekly signal detection of fever and medical visits monitors the log-likelihood ratio of cumulative events up to an expected level. For 2018, the expected rates for fever was 3% and for medical visits 1%. Maximum acceptable rates were set at 3% and 10% respectively. Two scenarios were developed based on expected and maximum acceptable rates for both events. The study also used estimates of AEFI rates that would have been reported. Observed rates for Fluvax and for other brands in 2010 were also incorporated to the doses administered to children aged 6 months to less than 5 years by brand. Using a SmartVax participation rate, expected responses were then estimated. Under scenario 1, the model predicted a >99% probability of fever safety signal being detected before the end of week 2. Under scenario 2, the prediction was >99% detection before the end of week 3 and >90% before the end of week 2. For medical

	attendance, under the most conservative scenario, the prediction was >99% detection before the end of week 6. Authors conclude that likely, the novel active safety surveillance system would have allowed earlier detection and suspension of Fluvax in 2010. They also speculate that this would have maintained confidence in seasonal influenza vaccination for young children. This is a well-written article that makes a convincing case for implementing active surveillance using SMS for novel vaccine products to monitor events that can occur within a week of administration. The main study limitations are based on the many assumptions required to generate the simulation parameters but those are well discussed. The only addition to the discussion could be elaborating further on indications for use of SmartVax-like systems and the link with vaccine confidence.

REVIEWER	Alexandra Pacurariu European Medicines Agency, Amsterdam, the Netherlands
REVIEW RETURNED	11-Aug-2019

GENERAL COMMENTS	Alexandra Dear Authors, I congratulate you for this important piece of work that test a newly implemented active surveillance system on a real case scenario and proves its utility. I have only two comments, also highlighted in the manuscript: - would it be possible to add 1 or 2 additional scenarios , with different expected rates and maximum acceptable rates, as the Scenario 2 ones is not informed by very strong evidence? - please comment on what other adverse events are suitable to be monitored through AuxVax Safety. Good luck, Alexandra The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Michael Stoto Georgetown Univ. & Harvard School of Public Health, USA
REVIEW RETURNED	11-Oct-2019

GENERAL COMMENTS	The potential for adverse events following immunisation (AEFI) (to use the authors' abbreviation) is an important problem, and no doubt contributes to the global problem of vaccine hesitancy. Consequently, monitoring systems such as the AusVaxSafety system are being developed in many countries. In this context, an evaluation of the performance of this system is very welcome. Nevertheless, there are two important problems with this analysis. First, although I understand why the authors' decision to focus on Western Australia in 2010, the results are very limited. Similarly, there are many different approaches to signal detection beyond FIR CUSUM methods and the specific parameters (e.g. control thresholds, minimally acceptable levels, etc.) that the authors tested. To be useful to a global audience, at a minimum some efforts should be made to at least describe how the results depend

	on the specific situations tested. Even better, the simulation should be extended to other settings. Second, the authors use the proportion of children in one study who experienced a fever and the proportion in another small study who sought medical attention to estimate the proportion of AEFIs that would have been reported in the AusVaxSafety system. I would imagine that the actual number of reports would be smaller for two reasons: (a) an SMS sent 3 – 5 days after immunisation is not likely to pick up events that occur later and (b) some fraction of vaccine recipients may not report their AEFIs.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
The only addition to the discussion could be elaborating further on indications for use of SmartVax-like systems and the link with vaccine confidence.

We have added a (penultimate) paragraph to the Discussion section which addresses this issue.

Reviewer 2:
Would it be possible to add 1 or 2 additional scenarios , with different expected rates and maximum acceptable rates, as the Scenario 2 ones is not informed by very strong evidence?
We have done additional simulations for both fever and medical attendance under an ultra-conservative Scenario 3 which has higher expected and maximum acceptable rates and therefore results in delayed signal detection. We have amended the manuscript and the figures to include details of these extra simulations.

Please comment on what other adverse events are suitable to be monitored through AuxVax Safety.
AusVaxSafety monitors reports of any adverse event following immunisation, any medical attendance for the adverse event, specific solicited adverse events (fever, injection site pain, injection site swelling and/or redness, rash, rigors, headache, vomiting, diarrhoea, non-responsiveness and/or loss of consciousness, seizure, tiredness, sleep pattern change, and irritability), and unsolicited ('other') adverse events, which can be reported by the participant in free text. Rates of these events are monitored weekly for influenza vaccine throughout the influenza vaccination season. Signal detection is performed on rates of medical attendance as a more objectively measured proxy for a serious adverse event; signal detection is also performed on rates of fever in children aged 6 months to <5 years principally because fever was an important indicator for the 2010 Fluvax safety signal.
AusVaxSafety currently only analyses adverse events reported in the 7 days following immunisation, but there is interest in an additional SMS message to capture reports of delayed-onset events requiring medical attention, such as those that occur in the weeks following immunisation with e.g. live vaccines, or events such as Guillain-Barré syndrome.
These details are largely covered in the papers (Leeb et al, Cashman et al) cited in the manuscript. However we can add the above paragraph to the current manuscript if the editor wishes.

Reviewer 3:
To be useful to a global audience, at a minimum some efforts should be made to at least describe how the results depend on the specific situations tested. Even better, the simulation should be extended to other settings.
The article describes how the AusVaxSafety system would have responded to a very specific real life vaccine safety event in 2010. Whereas it would be interesting to evaluate AusVaxSafety's performance in a variety of settings, such events occur rarely and we are not aware of another historical situation where we would have access to data enabling us to run similar simulations. We

think that a general evaluation of signal detection systems operating in different settings is beyond the scope of this article. We have added a dot point to the 'Strengths and Limitations' section to highlight this.

Second, the authors use the proportion of children in one study who experienced a fever and the proportion in another small study who sought medical attention to estimate the proportion of AEFIs that would have been reported in the AusVaxSafety system. I would imagine that the actual number of reports would be smaller for two reasons: (a) an SMS sent 3 – 5 days after immunisation is not likely to pick up events that occur later and (b) some fraction of vaccine recipients may not report their AEFIs.

We agree that the proportion of children with AEFIs solicited by AusVaxSafety may have been lower than that reported in the studies we used. It was for this reason that, in addition to the reported rates of fever and medical attendance in the studies, our evaluation also incorporated lower rates. Rather than an arbitrary reduction, we used the lower 95% confidence limits to capture the lower rates.

VERSION 2 – REVIEW

REVIEWER	Michael A Stoto Georgetown University, USA
REVIEW RETURNED	15-Dec-2019

GENERAL COMMENTS	As I indicated in my original review, the study is an evaluation of a single surveillance system in a particular place and specific event. Although well done, the results offer nothing of interest to others beyond those operating this system in Western Australia.