



## Safety and effectiveness of influenza vaccines

Unexpected safety signals and new data challenge our assumptions

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doi: 10.5694/mja14.01281

In this issue of the Journal, Wood and colleagues report the results of a study showing that the inactivated influenza vaccines currently licensed for use in children in Australia are reassuringly safe.<sup>1</sup> Study nurses at multiple sites around Australia telephoned parents to collect data on fever and other adverse events after vaccination. In the sample of 893 children aged 6 months to <10 years, the estimated risk of fever within 72 hours of influenza vaccine receipt was about 6% after the first or second dose. The risk of fever was higher if another vaccine was given at the same time. Only one febrile convulsion was reported, in a child with a known seizure disorder.

Until a few years ago, the safety of influenza vaccines was not a concern in Australia because no significant safety problem with their administration to adults or children had been reported through passive surveillance in more than 50 years. All this changed in 2010 when vaccines manufactured by bioCSL were shown to cause fever at 5–10 times previously accepted risk levels and febrile convulsions at 200 times higher levels.<sup>2</sup> These bioCSL vaccines must no longer be used in children aged under 5 years and should only be used with caution in children aged 5 to 9 years.

Research p 596

After extensive investigations over more than 3 years, bioCSL attributed the increased fever risk of the vaccine to a combination of its manufacturing process and strain changes in some years.<sup>3</sup> This is a potential concern because influenza vaccines often require strain changes — and a future strain change might also be associated with unexpected safety problems. Because only a few months elapse between strain selection and vaccine availability, there is no time for annual safety or efficacy trials of influenza vaccines. Efficacy is assumed from immunogenicity assays, based on older studies reporting the relationship between haemagglutination antibody titres and protection of 50% of vaccine recipients.<sup>4</sup> Post-infection ferret antisera and limited human data are used for specific strain selection.<sup>5</sup> Safety is assumed from the absence of prior reported adverse events. However, the experience of 2010 suggests the assumption that past safety predicts present safety might not be valid.

Assumptions about efficacy have also been questioned recently. As late as 2012, the World Health Organization asserted that influenza vaccines were 70%–90% effective.<sup>6</sup> While this may be true for live attenuated influenza vaccines given to children, it does not appear to be true for inactivated vaccines for any age group. Two recent meta-analyses report point estimates of efficacy for inactivated influenza vaccines against laboratory-confirmed influenza in community-based trials as 59%<sup>7</sup> and 52%–65%,<sup>8</sup> with the latter range depending on the degree of match between the circulating and vaccine strains. In Australia, observational studies that collected data over 4 or 5 years found point estimates of vaccine effectiveness of 62% in Victorian adults aged 20–64 years<sup>9</sup> and 65% in Western Australian children aged 6 months to 5 years.<sup>10</sup> However, vaccine effectiveness did not reach 50% in the Victorian community in 2012<sup>11</sup> or in Australian patients hospitalised with influenza in the 2 years before that.<sup>12</sup> Protection of older adults, who are targeted for vaccination, was particularly poor against influenza A(H3N2) in 2012.<sup>11</sup>

With the exceptions of an adjuvanted monovalent influenza vaccine manufactured by GlaxoSmithKline, which was used in Europe during the 2009 influenza pandemic and increased the risk of narcolepsy in children and young adults,<sup>13</sup> and the bioCSL vaccine given to children (not just in 2010),<sup>2,14</sup> most commentators accept that influenza vaccines are safe, based on the administration of many millions of doses over many years. However,

### Selected global studies monitoring annual influenza vaccine effectiveness

Study	Design and setting
<b>Southern hemisphere</b>	
Influenza Complications Alert Network (FluCAN) <sup>12</sup>	Pooled sentinel hospitals in Australia
Victorian sentinel general practice surveillance scheme <sup>9</sup>	Sentinel general practices in Victoria
Western Australian Influenza Vaccine Effectiveness (WAIVE) Study <sup>10</sup>	Emergency department presentations and hospital inpatients at Princess Margaret Hospital for Children, Perth
Southern Hemisphere Influenza Vaccine Effectiveness, Research and Surveillance (SHIVERS) study <sup>18</sup>	Population-based study in sentinel general practices and hospitals in Auckland, New Zealand
<b>Northern hemisphere</b>	
Canadian sentinel surveillance network <sup>19</sup>	Pooled sentinel general practices in Canada
Influenza Monitoring Vaccine Effectiveness (I-MOVE) network <sup>20</sup>	Pooled sentinel general practices in 6–8 European countries
US Influenza Vaccine Effectiveness (Flu VE) Network <sup>21</sup>	Pooled community-based sentinel research sites in the United States
Primary Health Care Sentinel Network and Network for Influenza Surveillance in Hospitals of Navarre <sup>22</sup>	Population-based study in sentinel general practices and hospitals in the Navarre region of Spain

unexpected safety signals show that such expectations will not always be met.<sup>2,13</sup>

Influenza vaccines with changed strains are considered to be variations of an existing vaccine, rather than new vaccines. As such, efficacy and safety studies are not required; nor are they practical in the time available. However, in the light of unexpected safety signals and sometimes low estimates of effectiveness, annual monitoring of the safety and effectiveness of influenza vaccines now seems like good public policy. It is therefore encouraging to see the safety study in this issue of the Journal.<sup>1</sup> Timely safety monitoring should become a funded routine component of the influenza vaccine program in Australia. Effectiveness monitoring may not be as timely as the new mobile phone and internet-based strategies for safety monitoring already being piloted in Australia,<sup>15-17</sup> but regular effectiveness monitoring should also become routine. Such monitoring is evolving throughout the world, including in Australia (Box), with many study sites able to derive timely interim effectiveness estimates using the case test-negative design.<sup>19-23</sup> Monitoring of both safety and effectiveness is needed to assess existing vaccines and vaccines that may be introduced in the near future, such as live attenuated influenza vaccines for children.

**Competing interests:** No relevant disclosures.

**Provenance:** Commissioned; externally peer reviewed.

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