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1   High-Dose Inactivated Influenza Vaccine is Associated with Cost Savings and Better Outcomes
2   Compared to Standard-Dose Inactivated Influenza Vaccine in Canadian Seniors

3
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Abstract

Seasonal influenza infects approximately 10-20% of Canadians each year, causing an estimated 12,200 hospitalizations and 3,500 deaths annually, mostly occurring in adults ≥65 years old (seniors). A 32,000-participant, randomized controlled clinical trial (FIM12; Clinicaltrials.gov NCT01427309) showed that high-dose inactivated influenza vaccine (IIV-HD) is superior to standard-dose vaccine (SD) in preventing laboratory-confirmed influenza illness in seniors. In this study, we performed a cost-utility analysis (CUA) of IIV-HD versus SD in FIM12 participants from a Canadian perspective. Healthcare resource utilization data collected in FIM12 included: medications, non-routine/urgent care and emergency room visits, and hospitalizations. Unit costs were applied using standard Canadian cost sources to estimate the mean direct medical and societal costs associated with each vaccine (2014 CAD). Clinical illness data from the trial were mapped to quality-of-life data from the literature to estimate differences in effectiveness between vaccines. Time horizon was one influenza season, however, quality-adjusted life-years (QALYs) lost due to death during the study were captured over a lifetime. A probabilistic sensitivity analysis (PSA) was also performed. Average per-participant medical costs were $47 lower and societal costs $60 lower in the IIV-HD arm. Hospitalizations contributed 91% of the total cost and were less frequent in the IIV-HD arm. IIV-HD provided a gain in QALYs and, due to cost savings, dominated SD in the CUA. The PSA indicated that IIV-HD is 89% likely to be cost saving. In Canada, IIV-HD is expected to be a less costly and more effective alternative to SD, driven by a reduction in hospitalizations.

Introduction

Seasonal influenza infects approximately 10-20% of the Canadian population each year. While most people recover within 7 to 10 days, severe illness can occur which causes an estimated 12,200 hospitalizations and 3,500 deaths annually.[1] These deaths primarily occur in adults aged 65 and older (herein referred to as seniors) who are more susceptible to downstream complications associated with influenza infection.[2, 3] Because seniors are at greater risk, the National Advisory Committee on Immunization (NACI) encourages all Canadian seniors to receive a vaccination each autumn.[1]

In the Canadian provinces, publicly-funded immunization programs provide free vaccine to all eligible members of the public. Trivalent inactivated influenza vaccine (IIV3) is the current vaccine funded for seniors in most provinces. A new high dose IIV3 vaccine (Fluzone High-Dose; IIV-HD) was approved September 2015 by Health Canada based on evidence from a randomized controlled trial (RCT) demonstrating improvements in efficacy over standard dose IIV3 vaccine (SD) in seniors.[4] The FIM12 study (Clinicaltrials.gov NCT01427309) showed IIV-HD to be superior to SD in preventing laboratory-confirmed influenza caused by any type or sub-type associated with clinically relevant illness in approximately 32,000 seniors (relative efficacy, 24.2%, 95% CI 9.7–36.5%).[5] Importantly, the study captured the seasonal variation typical of influenza activity as it was conducted over two sequential influenza seasons.[6-9] The 2011/12 season featured low levels of influenza circulation and a close match between the vaccine and circulating strains,[6] while the 2012/13 season was more severe with a poor match between vaccine and circulating strains.[7-9]

Although the acquisition cost of the IIV-HD is higher than that of SD, healthcare funding decision-makers need to consider all relevant costs of alternative interventions in relation to the resulting health outcomes. Formal techniques of economic evaluation, such as cost-effectiveness analysis (CEA), can be used to provide valuable information to decision makers regarding efficient allocation of finite healthcare resources. Using detailed data on healthcare utilization (HCU) and clinical outcomes collected from participants in the FIM12 trial, we have previously demonstrated IIV-HD to be a less costly and more effective alternative to SD in a United States (US)-focused cost-utility analysis (CUA) conducted from both a Medicare and societal perspective. Mean per-participant medical costs

3

68 (in 2014 USD) were lower in the IIV-HD group ($1376.72 USD) than in the SD group ($1492.64; difference –

69 $115.92). Further, the IIV-HD vaccine provided a gain in quality-adjusted life-years (QALYs; mean 8.1502

70 QALYs/participant) compared with the SD vaccine (8.1499 QALYs/participant) and, due to cost savings driven

71 primarily by fewer hospitalizations among subjects vaccinated with IIV-HD, dominated SD in the CUA.[10] The

72 objective of the current analysis was to determine if vaccination with the newly approved IIV-HD versus SD would

73 lead to similar economic benefits in Canada when Canadian unit costs and survival data were considered in place of

74 those used in our US analysis.

75

76 **Results**

77

78 Based on our analysis of HCU, per-participant visits to the emergency room (ER) and non-routine/urgent care visits

79 were slightly higher in the IIV-HD group than in the SD group, and slightly lower for prescription and non-

80 prescription medication use (Table 1, full analysis set). The mean per-participant number of hospitalizations was

81 0.0937 (1,498 hospitalizations in 15,990 participants) in the IIV-HD group and 0.1017 (1,629 hospitalizations in

82 15,993 participants) in the SD group, with averages of 0.4869 days and 0.5626 days for hospital length of stay

83 (LOS) per-participant, respectively.

84

85 **Table 1. Outcomes per participant**

86

87 Ninety-one percent of the total healthcare payer costs and 76% of the total societal costs were due to hospital

88 admissions. The total costs per participant were $60 higher in the SD group compared to the IIV-HD group. Further,

89 utilizing IIV-HD instead of SD, representing an additional expenditure of $25.97/participant, yielded a 181%

90 financial return ($47.15/participant) to the healthcare system mainly through reductions in hospital admissions

91 (Table 2).

92

93 **Table 2. Costs by resource item (in 2014 Canadian dollars/participant)**

94

95   The QALY analysis predicted that IIV-HD recipients would experience 7.5533 QALYs over the remainder of their

96   lifetime, whereas SD recipients would have 7.5530 QALYs, a difference of 0.0003 QALYs in favor of IIV-HD

97   (Table 2 and Table 4). For a cohort the size of the IIV-HD recipients in the clinical trial (N=15,990), this equates to

98   an additional 4.8 QALYs for the cohort. Since total costs were lower in the IIV-HD group and the health outcomes

99   were more favorable for IIV-HD, the cost-effectiveness analysis found that IIV-HD dominated (i.e., IIV-HD

100   provided more health at lower costs) SD vaccine from both the public payer and societal perspectives. A threshold

101   analysis determined that vaccination with IIV-HD continued to be cost-saving to the public payer up to a IIV-HD

102   price of approximately $79 per injection. IIV-HD remained dominant in the two sub-group analyses in study

103   participants with one or more comorbid conditions and in participants ≥75 years (societal perspective only). In the

104   public payer perspective analysis involving the subgroup of participants ≥75 years, a small incremental cost-

105   effectiveness ratio (ICER) of $82/QALY gained was obtained due to slightly higher costs (<$1) and QALYs

106   (0.0049) among participants in the IIV HD group compared to the SD group (Table 3).

107

108   **Table 3. Cost utility analysis**

109

110   In the cardiorespiratory condition analysis IIV-HD recipients gained more QALYs over their lifetime than SD

111   recipients and their healthcare system and societal costs were also less (Tables 2-4). The total costs per participant

112   were $29 lower in the IIV-HD group than they were in the SD group. The expenditure required to administer IIV-

113   HD instead of SD ($25.97/participant) yielded an 80% financial return ($20.65/participant) to the healthcare system

114   (Table 3), and vaccination with IIV-SD remained cost-saving up to a cost per injection of approximately $53.

115   Further, IIV-HD remained dominant in the cost-effectiveness analysis including all sub-group analysis (Table 4).

116

117   ICERs computed in the PSA revealed that 89% of the points in the full-analysis set and 83% of the points in the

118   cardiorespiratory analysis set clustered in the lower quadrants of the plot (Figure 1). Further, in the cardiorespiratory

119   set 80% of the samples clustered in the lower right quadrant. These results illustrate that IIV-HD is less costly than

120   SD with high certainty. The cardiorespiratory analysis also illustrates that reduction in cardio-respiratory

121   complications provide much of the health benefits offered by IIV-HD.

122

123 **Figure 1. Scatterplots representing the statistical uncertainty through a 1,000 bootstrapped samples**

124

125 ## Discussion

126

127 In this Canadian economic evaluation based on a RCT of approximately 32,000 seniors, we found that IIV-HD was

128 a cost-saving alternative to SD, the current standard of care for ambulatory seniors in most provinces, and this

129 conclusion was robust in the face of statistical uncertainty. From the societal perspective, savings were estimated to

130 be $60 per IIV-HD participant when considering the full analysis set and $29 per IIV-HD participant when

131 considering the cardiorespiratory condition analysis set. Savings to the healthcare payer were slightly less, at

132 approximately $47 and $21 per IIV-HD participant, respectively. Since the price of IIV-HD has not been established

133 in Canada yet, we used the US price assuming a 1:1 exchange rate (based on exchange rates current at the time the

134 study was conducted; $31.81 per injection); however, the actual Canadian launch price will depend on a number of

135 factors such as, for example, global supply and demand constraints and changes in exchange rates. Therefore, we

136 conducted threshold analyses on IIV-HD price which determined that the price could increase to just under $79 (full

137 analysis set) and $53 (cardiorespiratory condition analysis set) per injection and still be cost saving to healthcare

138 payers. As noted, the majority of the savings generated by IIV-HD were driven by reductions in cardiorespiratory

139 hospitalizations plausibly related to influenza.

140

141 Our previous analysis based on the same RCT, but conducted from the Medicare and societal perspectives in the US,

142 found similar results, though the magnitude of the cost savings was higher in the US (e.g., $128 and $80 USD

143 (2014) per IIV-HD participant based on the full and cardiorespiratory condition analysis sets, respectively). This

144 difference was driven by the fact that hospital per diems were, on average, approximately 51% (or ~$1,400/day

145 without adjustment for exchange rate) lower in Canada than in the US.[10] The only other IIV-HD cost-effectiveness

146 study identified in the literature was a mathematical modeling study (discussed in depth in our previous publication

147 [10]) which predicted that the IIV-HD would be a cost-effective alternative to SD (incremental cost-effectiveness ratio

148 $5,399 USD/QALY gained).[11]

149

150   A key feature of this study is that it uses a randomized head-to-head design (FIM12), to define causality between the

151   vaccines and healthcare resource consumption. The FIM12 RCT was sufficiently large to observe the cost-saving

152   signal generated by IIV-HD from background noise (heterogeneous healthcare expenditures amongst seniors).

153   Further, the healthcare cost data we used are directly applicable to Canadian public payers as they were obtained

154   from Ontario sources, which is the largest province by population in Canada.

155

156   The study also had a number of limitations beyond those previously discussed.[10] As noted, FIM12 was a

157   multinational study, however, only 5% of participants were enrolled in Canada while the remaining 95% of

158   participants were from the US. For our analysis, all HCU data were pooled across all patients even though it is

159   conceivable that HCU may potentially have been affected by differences in the structure of healthcare delivery

160   systems, practice patterns, and the availability and access to healthcare services between the two countries.

161   Statistical testing was conducted prior to data pooling, which did not detect heterogeneity among HCU between

162   countries. Therefore, it was justified to pool the trial data for all analyses.

163

164   Another limitation is that the collection of per diems for assignment to each hospitalization required some

165   simplifying techniques to manage the data collection burden. As has been explained, hospitalizations were

166   categorized into a manageable number of groups using the Medical Dictionary for Regulatory Activities (MedDRA)

167   coding system, which were first mapped to an International Classification of Diseases, Ninth Edition, Clinical

168   Revision (ICD-9-CM) code(s) and then, specifically for the Canadian analysis, to an ICD Tenth Edition (ICD-10)

169   code(s) for per diem cost collection and assignment from the Ontario Case Costing Initiative (OCCI) database.

170   Although this approach was used consistently across all hospitalizations regardless of vaccine group, it is possible

171   that some specificity was lost during the grouping and two-step mapping process. To limit the potential for error

172   and/or inaccurate assignment of codes, the same analyst with medical training completed both steps of the mapping

173   exercise, and all mappings were reviewed by a physician at Sanofi Pasteur.

174

175   Finally, it is worth noting that our study was a comparison of vaccination with IIV-HD against SD, which is the

176   current standard of care for seniors in most Canadian provinces. However, other vaccines such as standard dose

177   quadrivalent inactivated influenza vaccine and adjuvanted trivalent inactivated influenza vaccine are used for seniors

178 in some provinces and long-term care facilities. Since our analysis was based on data collected in a head-to-head

179 trial comparing only IIV-HD versus SD, we did not consider the cost-effectiveness of IIV-HD compared to other

180 vaccines.

181

182 In conclusion, after accounting for the price difference between IIV-HD and SD, vaccination with IIV-HD resulted

183 in cost savings to the public payer and to society in Canada. This was driven by a reduction in the number of

184 hospitalizations. As the clinical benefits are higher for IIV-HD and associated total costs are lower, it dominated SD

185 in the CUA.

186

Patients and Methods

187

188

Analytic approach

189

190

191 The methods developed for this analysis of the economic impact of IIV-HD versus SD in Canada as measured in the

192 FIM12 trial[5] have been described in detail in a previous publication of a CUA conducted for the US.[10] Here we

193 provide a general overview of these analytic methods along with a detailed description of the adaptations made to

194 the analysis specifically for the Canadian setting.

195

196 Briefly, FIM12 was a head-to-head RCT of IIV-HD versus SD (randomized 1:1) that enrolled approximately 32,000

197 seniors over two influenza seasons (2011/2012 and 2012/2013). A surveillance program captured HCU data for all

198 study participants, including use of prescription and non-prescription medications (limited to

199 antipyretics/analgesics/non-steroidal anti-inflammatory drugs, antivirals, and antibiotics), emergency room ER

200 visits, non-routine/urgent care visits, and hospitalizations, if they occurred within 30 days after any study respiratory

201 illness (the frequency and types of respiratory illnesses have been described in the original trial publication[5]). In

202 addition, hospitalizations resulting from serious events (serious events were defined as events: leading to death or

203 hospitalization (or its prolongation); considered as life-threatening or medically important; or resulting in disability)

204 were captured for all participants and for the duration of the study, regardless of their occurrence in relation to a

205 study respiratory illness.[5]

206

207 Our primary analysis estimated Canadian public healthcare system expenditures based directly on the HCU data

208 collected in each arm of the FIM12 study. In exploratory analyses, we also examined differences in costs not

209 covered by the public payer, including out-of-pocket costs for non-prescription medications and work force

210 productivity losses. Further, we estimated the incremental cost-utility of IIV-HD versus SD. To perform the CUA,

211 we modeled the expected impacts of the medical events captured in FIM12 on quality of life (QoL) during the

212 clinical trial period and throughout the life expectancy of the study cohort. Modeled health outcomes that extended

213 beyond the study duration were discounted at five percent annually; costs were not discounted since they were based

214 only on HCU reported during the trial period and did not extend beyond one year.[12] All costs were reported in 2014

215 Canadian dollars.

216

217 **Costing analysis**

218

219 Although FIM12 was a multinational study, only 5% of participants were enrolled in Canada while the remaining

220 95% of participants were from the US. Prior to pooling HCU data across all participants, tests of significance were

221 performed to detect potential differences in utilization patterns between the US versus Canada. Specifically, we

222 assessed the impact of vaccine strategy on the total intensity of HCU across countries using the total medical cost, in

223 a single currency (2014 USD), for each subject as a proxy measure for overall HCU intensity. A regression analysis,

224 using a gamma regression model, was conducted with HCU intensity (cost) as the dependent measure and the

225 independent measures were vaccine group, country, and an interaction term between vaccine group and country. It is

226 the interaction term, or whether there is a similar effect of study treatment on the incremental cost difference across

227 countries, that determines whether it is appropriate to pool all participants in a straightforward way.[13] Because there

228 was not a significant interaction between vaccine group and country with outcome considered to be the total medical

229 cost (p=0.96; i.e., heterogeneity among HCU was not detected between countries), it was justified to pool the trial

230 data for all analyses.

231

232 The pooled healthcare resources for all subjects in the trial were valued using unit prices relevant to Canada from

233 standard sources. In cases where costs were not available in 2014 dollars, they were inflated using the healthcare

9

234   component of the consumer price index (CPI).[14] Total costs were calculated from the quantity of resources

235   consumed (for example, number of days hospitalized) and the unit cost per resource. The analysis from the public

236   payer perspective considered the following costs: vaccine, prescription medication, medical visits, and

237   hospitalizations. The analysis from the societal perspective additionally included the costs of non-prescription

238   medication and lost work force productivity.

239

240   Since IIV-HD was not marketed in Canada at the time of the study, it was assumed the list price would be the same

241   as in the US (since the USD and Canadian dollar were approximately at par when the study was conducted

242   (2013/2014)) obtained from the Centers for Medicare & Medicaid Services (CMS) Seasonal Influenza Vaccines

243   Pricing List.[15] The cost of SD was provided by Sanofi Pasteur.[16] The cost per unit for each prescription medication

244   was obtained from the Ontario Drug Benefit Formulary (used as a proxy for Canada).[17] The cost per prescription

245   included an 8% upcharge and $8.83 dispensing fee per length of treatment.[18] The unit cost for non-prescription

246   medications (societal perspective only) was obtained from a large Canadian pharmacy chain.[19]

247

248   The unit costs for respiratory illness-related ER and non-routine/urgent care visits were obtained from Canadian

249   Institute for Health Information (CIHI) reports.[20, 21] The costs of hospitalizations were calculated by multiplying the

250   hospital LOS by the unit cost per day (per diem). To estimate the per diem cost, diagnosis codes related to

251   hospitalizations were grouped into preferred terms under the MedDRA coding system and mapped to the ICD-9-CM

252   codes (for the purpose of assigning costs in the original US analysis). The ICD-9-CM codes were then mapped to

253   ICD-10 codes for the purpose of extracting and assigning per diem costs from the OCCI's on-line database.[22]

254

255   Productivity costs were imputed using methods described by Molinari et al. in which the number of medical visits

256   per participant represented the number of days of productivity lost (at a ratio of one visit: one day of lost

257   productivity).[23] The number of days of lost productivity was valued at the average daily wage for Canadian

258   employees in 2014.[24] All unit costs used in the analysis are provided in Table 4.

259

260   **Table 4. Unit Costs of Resource Items (2014 Canadian dollars)**

261

Cost-effectiveness

An ICER was calculated for IIV-HD versus SD. The ICER was defined as $(Cost_{IIV-HD} - Cost_{SD})/(Outcomes_{IIV-HD} -$

$Outcomes_{SD})$. The costs and outcomes were the total costs and outcomes from each arm of the FIM12 trial. We also

calculated ICERs for the following two subgroups: participants with one or more co-morbid condition (N=21,502)

and participants ≥75 years of age (N=10,839).

The outcome of the CUA was the QALY. To estimate the number of QALYs in each vaccine arm we first estimated

the total number of life-years (LYs) per arm. We used age- and gender-specific Canadian life expectancy data from

Statistics Canada to estimate the LYs for study participants.[25] When weighted according to the FIM12 gender

distribution (43% male, 57% female), the mean life expectancy for subjects in FIM12, prior to adjustments for

discounting and deaths experienced during the trial was 9.9 years. After applying an annual discount rate of 5%,

mean life expectancy for subjects in FIM12 was 7.6 years. For each subject who died during the study, their

remaining length of life was calculated based only on the amount of time for which they survived following

vaccination (date of death - date of vaccination + 1).

Since QoL data were not collected in the FIM12 trial, we adjusted the LYs to estimate QALYs using QoL data

specific to the participant's age, gender, and the medical events they experienced during the study. Additional details

regarding the methodology including the utility and disutility values applied in our analysis have been reported in

our previously published CUA.[10]

Subgroup and uncertainty analysis

As FIM12 was not powered for the purpose of this economic evaluation, it was possible that the economic benefit of

IIV-HD would be difficult to detect due to the multiple non-influenza related events collected in the FIM12 study.

To overcome this and to increase the specificity of our analysis we planned a cardiorespiratory condition analysis

that accounted for a subset of clinical outcomes selected by study clinicians before unblinding the study based on the

plausibility of their relation to influenza. Outcomes groupings included pneumonia events, asthma/chronic

obstructive pulmonary disease/bronchial events, influenza events (serious laboratory-confirmed influenza diagnosed

290   outside study procedures by a participant's healthcare provider), other respiratory events, coronary artery events,

291   congestive heart failure events, and cerebrovascular events. A more granular listing of the conditions included in this

292   subgroup and the methods used to identify these events has previously been published by DiazGranados et al.,

293   2015.[26]

294

295   To explore the impact of statistical uncertainty on the results we conducted a bootstrapping analysis of the trial data

296   with replacement as described in our previous work.[10] Results are presented as a scatterplot on a cost-effectiveness

297   plane.[27]

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Conflicts of Interest

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