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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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19 **Abstract**

20

21 Seasonal influenza infects approximately 10-20% of Canadians each year, causing an estimated 12,200
22 hospitalizations and 3,500 deaths annually, mostly occurring in adults ≥ 65 years old (seniors). A 32,000-participant,
23 randomized controlled clinical trial (FIM12; Clinicaltrials.gov NCT01427309) showed that high-dose inactivated
24 influenza vaccine (IIV-HD) is superior to standard-dose vaccine (SD) in preventing laboratory-confirmed influenza
25 illness in seniors. In this study, we performed a cost-utility analysis (CUA) of IIV-HD versus SD in FIM12
26 participants from a Canadian perspective. Healthcare resource utilization data collected in FIM12 included:
27 medications, non-routine/urgent care and emergency room visits, and hospitalizations. Unit costs were applied using
28 standard Canadian cost sources to estimate the mean direct medical and societal costs associated with each vaccine
29 (2014 CAD). Clinical illness data from the trial were mapped to quality-of-life data from the literature to estimate
30 differences in effectiveness between vaccines. Time horizon was one influenza season, however, quality-adjusted
31 life-years (QALYs) lost due to death during the study were captured over a lifetime. A probabilistic sensitivity
32 analysis (PSA) was also performed. Average per-participant medical costs were \$47 lower and societal costs \$60
33 lower in the IIV-HD arm. Hospitalizations contributed 91% of the total cost and were less frequent in the IIV-HD
34 arm. IIV-HD provided a gain in QALYs and, due to cost savings, dominated SD in the CUA. The PSA indicated
35 that IIV-HD is 89% likely to be cost saving. In Canada, IIV-HD is expected to be a less costly and more effective
36 alternative to SD, driven by a reduction in hospitalizations.

37

38 **Keywords:** influenza, high-dose inactivated influenza vaccine, Fluzone, cost-utility, cost-effectiveness

39

40 Introduction

41

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

48

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

60

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

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

187 **Patients and Methods**

188

189 **Analytic approach**

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 trial⁵ 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 publication⁵). 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

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

262 **Cost-effectiveness**

263

264 An ICER was calculated for IIV-HD versus SD. The ICER was defined as $(Cost_{IIV-HD} - Cost_{SD}) / (Outcomes_{IIV-HD} -$
265 $Outcomes_{SD})$. The costs and outcomes were the total costs and outcomes from each arm of the FIM12 trial. We also
266 calculated ICERs for the following two subgroups: participants with one or more co-morbid condition (N=21,502)
267 and participants ≥ 75 years of age (N=10,839).

268

269 The outcome of the CUA was the QALY. To estimate the number of QALYs in each vaccine arm we first estimated
270 the total number of life-years (LYs) per arm. We used age- and gender-specific Canadian life expectancy data from
271 Statistics Canada to estimate the LYs for study participants.²⁵ When weighted according to the FIM12 gender
272 distribution (43% male, 57% female), the mean life expectancy for subjects in FIM12, prior to adjustments for
273 discounting and deaths experienced during the trial was 9.9 years. After applying an annual discount rate of 5%,
274 mean life expectancy for subjects in FIM12 was 7.6 years. For each subject who died during the study, their
275 remaining length of life was calculated based only on the amount of time for which they survived following
276 vaccination (date of death - date of vaccination + 1).

277

278 Since QoL data were not collected in the FIM12 trial, we adjusted the LYs to estimate QALYs using QoL data
279 specific to the participant's age, gender, and the medical events they experienced during the study. Additional details
280 regarding the methodology including the utility and disutility values applied in our analysis have been reported in
281 our previously published CUA.¹⁰

282

283 **Subgroup and uncertainty analysis**

284 As FIM12 was not powered for the purpose of this economic evaluation, it was possible that the economic benefit of
285 IIV-HD would be difficult to detect due to the multiple non-influenza related events collected in the FIM12 study.

286 To overcome this and to increase the specificity of our analysis we planned a cardiorespiratory condition analysis
287 that accounted for a subset of clinical outcomes selected by study clinicians before unblinding the study based on the
288 plausibility of their relation to influenza. Outcomes groupings included pneumonia events, asthma/chronic
289 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

298
299
300

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301 **Conflicts of Interest**

302

303 Funding for this study was provided by Sanofi Pasteur.

304

305 AC and CD conceived the study. AC, DB, CD, MM, EY and MD designed the study. DB and MM conducted the
306 analysis. AC, DB, CD, MM, EY and MD interpreted the results. DB wrote the initial draft of the manuscript. AC,
307 DB, CD, MM, EY and MD critically revised the manuscript and approved the final version. AC had full access to all
308 the data in the study and had final responsibility for the decision to submit the publication.

309

310 AC and CD are employees of Sanofi Pasteur (SP). DB and MM are employees of Optum. MD was a Consultant at
311 Optum at the time this study was conducted. Optum was contracted by SP to conduct this study. EY was an
312 employee of inventive Health Clinical during the study. Inventive Health Clinical was contracted by SP to work on
313 clinical analysis of the FIM12 trial.

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