Assessing health opportunity costs for the Canadian health care systems

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Summary

The economic evaluation of health care interventions including new health technologies such as branded pharmaceuticals requires an assessment of whether the improvement in health outcomes they offer exceeds the improvement in health that would have been possible if the additional resources required had, instead, been made available for other health care activities. Therefore, some assessment of these health opportunity costs is required if the best use is to be made of the resources available for health care. It is this assessment of health opportunity costs that indicates the maximum that health care systems can afford to pay for the benefits offered by new drugs protected by patent. This represents the temporary monopoly price that could be paid if health care systems choose not to use their monopsony power and is consistent with price regulation that upholds the protections offered by existing patents.

This report provides a brief review of the literature on the assessment of health opportunity costs, outlines how existing estimates of the effect of changes in health expenditure on mortality, as well as survival and morbidity, can be used to provide some initial assessment of a cost-effectiveness threshold that reflects likely health opportunity costs across the different provinces of Canada. The range of possible estimates based on existing work are discussed and some suggestions are made of how further research could provide estimates that more closely reflect evidence of the health effects of health care expenditure in the Canadian provinces.

Based on the balance of the evidence currently available some recommendations can be made. There is a wide range of potential cost per DALY averted estimates for Canada ($20,000 to $100,000 per DALY averted in Table 4), with the lower estimates associated with more recent work using within country rather than country level data. Therefore, it is the lower end of this range that might be regarded as most plausible, so ***a cost per DALY threshold is likely to be less than $50,000 for Canada as a whole***.

A measure of heath benefit more appropriate to Canada would be QALY gained rather than DALYs averted. However, currently there are no estimates of QALY burden of disease which would allow estimates of the mortality effects of changes in expenditure to be used to estimate a cost per QALY threshold. Nonetheless, estimates of the DALYs averted from changes in expenditure are on average likely to be similar or less than the QALY gained. Therefore, ***a cost per QALY threshold is likely to be similar or lower than a cost per DALY averted threshold.***

This is consistent with the range of implied cost per QALY gained for Canada based on the analysis in Woods et al 2016. Estimates based on this analysis have been adopted in Norway while further research using within country data are explored. Using this approach would provide a cost per QALY threshold for Canada of $28,089.

Therefore, taking all this evidence together suggests that ***a cost per QALY threshold of $30,000 per QALY would be a reasonable assessment of the health effects of changes in health expenditure for Canada as a whole and is likely to be similar across most provinces***.

1. Introduction

Evidence of the expected costs and health effects of making a new health technology available to specific populations in a particular setting and health care system (HCS) are often summarised as incremental cost-effectiveness ratios (ICERs). These ratios are often expressed as the cost per Quality Adjusted Life Year (QALY) gained or the cost per Disability Adjusted Life Year (DALY) averted (Salomon et al. 2012). These measures provide a useful summary of how much additional resource is required to achieve a measured improvement in health (the additional cost required to gain one QALY or to avert one DALY). Whether the cost per QALY gained or DALY averted offered by an intervention is regarded as worthwhile requires a comparison with a cost-effectiveness 'threshold'. An effective intervention will only improve health outcomes overall (i.e., produce a positive net health benefit) if the additional health benefits exceed the health opportunity costs associated with the additional health care costs that must be found from existing commitments or that use additional expenditure that could have been devoted to other health care activities. Such an assessment of health opportunity cost reflects the maximum a HCS can afford to pay for the health benefits that a new health technology offers, without reducing health outcomes overall. Therefore, an evidence based assessment of health opportunity costs is critical to the appropriate pricing of new branded pharmaceuticals while they are protected by patent (Claxton et al. 2008; Claxton et al. 2011).

A cost per QALY 'threshold' that reflects the health opportunity costs of changes in health expenditure indicates the maximum that health care systems can afford to pay for the benefits offered by new drugs protected by patent. It represents the value of the innovation to the health care system, or the temporary monopoly price that could be paid while it is protected by patent. Therefore, establishing prices for new drugs based on an assessment of their health benefits and a cost per QALY threshold that reflects health opportunity costs is consistent with upholding the protections offered by patents. It does mean that the value of the innovation will be appropriated by the manufacturer in the short run before the patent expires. However, on patent expiry the health care system starts to appropriate the value of the innovation as cheaper generic versions of the original brand enter a competitive generics market. Prescribing can then switch to cheaper generic versions of the old brand and/or any new patented drugs that enter are compared to the cheaper generic versions of the old brand when establishing how much health care systems can afford to pay for the additional benefits they offer. Therefore, setting prices for new drugs that are protected by patent based on an assessment of health opportunity costs, only until the patent expires, ensures that the value of innovation is shared between manufacturers and health care systems in a way that is consistent with existing levels of patent protection.

Estimating health opportunity costs

A persistent problem has been that the cost-effectiveness 'thresholds' (e.g. cost per QALY or cost per DALY thresholds) recommended or cited by decision making and advisory bodies (both national and supra-national) reflect a lack of conceptual clarity about what they ought to represent and what type of evidence might inform their assessment (Revill et al. 2014; Culyer 2016). As a consequence these values are not evidence based and have simply become established norms or implied values, which describe the criteria used to judge cost-effectiveness (Claxton, Sculpher, et al. 2015). Other proposed thresholds reflect a view of what value ought to be placed on improvements in health.

They imply what health care expenditure ought to be (the social demand for health) rather than an evidence based assessment of health opportunity costs given actual levels of expenditure, i.e. a 'supply side' estimate of the amount of health that a HCS currently delivers with more or less resources.

The problem of estimating a cost-effectiveness 'threshold' that represents expected health opportunity costs is the same as estimating the relationship between changes in health care expenditure and health outcomes. Estimates of the marginal productivity of health expenditure in producing health (QALYs) are becoming available for some high income countries based on approaches to estimation which exploit within country data (Martin et al. 2008; Vallejo-Torres et al. 2016; Edney et al. 2017; Claxton, Martin, et al. 2015). This evidence from national HCS contexts in high income countries can be used to give some indication of possible values in other contexts (Woods et al. 2016) based on estimates of the income elasticity of demand for health and assumptions about the relative underfunding of HCS (i.e., the shadow price for public expenditure on health). Another approach has taken estimates of the effect of health care expenditure on health outcomes based on country level data (typically expressed as elasticities) and applied these to country-level baseline health and demographic data to generate overall cost per DALY 'thresholds' (Ochalek et al. 2015).

Canada has a longstanding health technology assessment agency in CADTH that makes use of cost-effectiveness evidence in the form of ICERs. However, like in many other jurisdictions, there is no explicit and empirically-informed 'threshold' that reflects the likely health opportunity costs so it is not possible to assess the likely net health effect of approving a new health technology or establish what price ought to be paid for new pharmaceuticals protected by patent. Although Canada is similar to countries, such as the UK, in terms of the availability of high quality health and health care data, there are, as yet, no estimates of the marginal productivity of health care expenditure using Canadian data. In addition a significant difference exists between the HCS of Canada and the UK, in that decisions in Canada are more likely to be made, not at the national level, but at the level of individual provinces. This report details the methodology that was used to generate province-level estimates of health opportunity costs (cost per DALY 'thresholds'). In broad terms, this involved tailoring the approach taken by Ochalek et al. (2015) to consider health opportunity costs that occur at the provincial level using province specific data on health expenditure, epidemiology and demographics.

2. Methods

The effect of different levels of health care expenditure on mortality outcomes has been investigated in a number of published studies using country level data, many including high as well as low and medium income countries (Gallet & Doucouliagos 2017). The challenge is to control for all the other reasons why mortality might differ between countries to isolate the causal effect of differences in health expenditure (Nakamura et al. 2016). This is a particular challenge even if available measures are complete, accurate and unbiased because health outcomes are likely to be influenced by expenditure (increases in expenditure improves outcomes), but outcomes are also likely to influence expenditure (poor outcomes prompt greater efforts and increased expenditure). This problem of endogeneity, as well as the inevitable aggregation bias, risks underestimating the

health effects of changes in expenditure. Instrumental variables have been used in a number of studies to try and overcome this problem and estimate outcome elasticities for all cause adult, maternal and child mortality (Bokhari et al. 2007 among others). The Bokhari et al (2007) model specification applies an instrumental variable approach to cross-sectional data from the year 2000 for 127 countries and models both public expenditure on health and a country's GDP as endogenous variables (both in per capita terms). Specifically, the identification strategy of Bokhari et al (2007) employs two instrumental variables: military expenditure per capita of neighbouring countries and a measure of institutional quality. These represent typical instrumental variables following in the tradition of earlier papers such as Filmer & Pritchett (1999). In addition, Bokhari et al (2007) perform a logarithmic transformation of their data so that coefficients can be interpreted as elasticities, and allow for the outcome elasticity with respect to expenditure of countries to vary by two variables: the level of infrastructure (proxied by 'paved roads per unit of area') and shock in donor funding (measured by absolute deviation in current donor funding from historical mean).

This approach to estimation using country level data can provide country specific cost per DALY averted values by applying estimated elasticities, which take account of measures of a country's infrastructure and changes in donor funding, to country specific mortality rates, conditional life expectancies and population distribution (all by age and gender) as well as estimates of disability burden of disease and total health care expenditure. We re-estimate the effect of changes in expenditure using Bokhari et al (2007)'s dataset after expanding the dataset to include under-5 mortality from the World Bank in addition to adult male and adult female mortality, which enables greater coverage of the population, as well as: i) a measure of survival, years of life lost (YLLs); ii) a measure of morbidity, years of life disabled (YLDs); and iii) DALYs, a generic measure of overall ill health, from the Global Burden of Disease database. Although elasticities are estimated at the country level, they differ only with respect to the interaction of measures of infrastructure and donor funding. The estimated elasticities for Canada (see Table 2) are applied to province specific data on health expenditure, epidemiology and demographics, i.e., in the absence of elasticity estimates at the provincial level the estimate for Canada are assumed to be common across the provinces. Nonetheless, the health effects of changes in health expenditure will differ across provinces due to differences in health expenditure, epidemiology and demographics.

There are four ways in which the estimated elasticities in Table 2 can be used to estimate the likely DALYs averted as a consequence of a 1% change in health expenditure in each province, *i*. Each of the four ways in which a cost per DALY can be estimated are summarised in Table 1 and are briefly described below, with details of the data used reported in Appendix A.

Table 1. Alternative approaches to calculating DALYs averted

<table>
<tr><th></th><th></th><th>DALY 1</th><th>DALY 2</th><th>DALY 3</th><th>DALY 4</th></tr>
<tr><td>Survival effects (YLLs averted)</td><td></td><td>Based on indirectly estimating effects on survival from mortality (A)</td><td colspan="2">Directly estimated (D)</td><td rowspan="3">Directly estimated (G)</td></tr>
<tr><td rowspan="2">Morbidity Effects (YLDs averted)</td><td>Direct effect</td><td>Uses indirectly estimated effects on survival from mortality as a surrogate for morbidity effects (B)</td><td>Uses directly estimated survival effects as a surrogate for morbidity effects (E)</td><td rowspan="2">Directly estimated (F)</td></tr>
<tr><td>Indirect effect</td><td colspan="2">Uses average overall population health as a surrogate for increase in YLD burden associated with increase in YLLs averted (C)</td></tr>
</table>

DALY 1

The first estimate is based only on estimates of the mortality effects of changes in expenditure. As these are the most prevalent estimates available across the literature, this enables DALY 1 to be calculated using elasticities from various sources, such as the all-cause mortality elasticities that have been estimated in the UK as part of work on health opportunity costs (Claxton et al. 2017; Andrews et al. 2017).

The estimated elasticity for children under-5, $\in^{mortality}$, can be applied to the number of deaths observed in this age group in each province to provide an estimate of the number of deaths averted as a consequence of a 1% change in provincial health expenditure.

(1) $directly\ estimated\ deaths\ averted_i^{0-4} = 1\% * \left|\epsilon_{Canada}^{mortality^{0-4}}\right| * deaths_i^{0-4}$

Similarly, the estimated elasticities for male and female adults (ages 15-60) are applied to observed deaths by age and gender in each province, i.e., assuming that the proportionate effect on mortality applies equally across age groups within 15-60 age range.

(2) $directly\ estimated\ deaths\ averted_i^{15-60} = 1\% * \left|\epsilon_{Canada}^{mortality^{15-60}}\right| * deaths_i^{15-19} + \cdots + 1\% * \left|\epsilon_{Canada}^{mortality^{15-60}}\right| * deaths_i^{55-60}$

Once the likely deaths averted by a 1% change in health expenditure have been estimated in this way (see (1) and (2), the survival effects can be established by applying conditional life expectancy (CLE) at age of death to each death averted within each age group (see (3) and (4)). An estimate of survival gains of a change in health expenditure based on mortality effects (mortality based YLL averted) is simply the sum of these effects (5).

(3) $mortality\ based\ YLL\ averted_i^{0-4} = CLE_i^{0-4} * deaths\ averted_i^{0-4}$

(4) $mortality\ based\ YLL\ averted_i^{15-60} = CLE_i^{15-19} * deaths\ averted_i^{15-19} + CLE_i^{20-24} * deaths\ averted_i^{20-24} + \cdots + CLE_i^{55-59} * deaths\ averted_i^{55-59}$

(5) $mortality\ based\ YLL\ averted_i^{0-4\ \&\ 15-60} = mortality\ based\ YLL\ averted_i^{0-4} + mortality\ based\ YLL\ averted_i^{15-60}$

However, this measure (5) excludes potential survival effects in ages 5-14 years and also those over the age of 60. To try to reflect the possible survival effects across all ages the estimate of the YLL averted in (5) can be adjusted using the YLL in these age group as a proportion of the YLL across all ages, σ_i (6),

(6) $mortality\ based\ YLL\ averted_i^{all\ ages} = \frac{mortality\ based\ YLL\ averted_i^{0-4\ \&\ 15-60}}{\sigma_i}$

where,

(7) $\sigma_i = \frac{YLL_i^{0-4} + YLL_i^{15-60}}{YLL_i^{all\ ages}}$

The YLL for each age group is simply the observed deaths in that age group multiplied by the conditional life expectancy for that age, i.e., it represents the survival burden of disease in each age and gender group. For example,

(8) $YLL_i^{0-4} = CLE_i^{0-4} * absolute\ deaths_i^{0-4}$

(9) $YLL_i^{15-60} = CLE_i^{15-19} * absolute\ deaths_i^{15-19} + CLE_i^{20-24} * absolute\ deaths_i^{20-24} + \cdots + CLE_i^{55-59} * absolute\ deaths_i^{55-59}$

The $YLL_i^{all\ ages}$ is calculated in a similar way to (8) and (9), as the sum of the product of absolute deaths and conditional life expectancy across all age groups in the population.

Therefore, the extrapolation of the survival effects from those age groups where mortality effects can be estimated (5) to all age groups in the population (6) assumes that the survival effects of changes expenditure are in proportion to the survival burden of disease at each age.

There are likely to be direct and indirect effects on morbidity of changes in expenditure. For example, changes in expenditure that affect mortality and survival are also likely to have an effect on morbidity through the prevention and treatment of disease (i.e., a direct effect decreasing YLD burden). However, an indirect effect may also be present as reductions in mortality and the resulting increased survival is likely to increase the number of years during which morbidity is experienced.

To calculate the possible direct effect we assume that the effect of changes in expenditure on morbidity is proportional to the effect on survival (B in Table 1), i.e., assuming that the estimated effects on the mortality burden of disease can be used as a surrogate for likely effects on morbidity burden where these effects have not been directly estimated. Since YLD data are not available by province, the ratio of YLD to YLL in Canada, γ, is applied to estimates of the province specific survival effects from (6) (see the first term of (12) below).

(10) $$\gamma = \frac{YLD_{CANADA}^{all\ ages}}{YLL_{CANADA}^{all\ ages}}$$

To account for the indirect effect of increasing the number of years during which morbidity is experienced due to the survival effects, we apply the per capita YLD burden for each province to the province specific survival effects (see the second term in (12) below and C in Table 1), Since province specific estimates of YLD are not available we assume that YLD are distributed across provinces in the same proportion as YLL (11), i.e., assuming that the morbidity burden of disease is likely to be higher (lower) where the survival burden is higher (lower).

(11) $$per\ capita\ YLD\ burden_i^{all\ ages} = \left(\frac{YLL_i^{all\ ages}}{YLL_{CANADA}^{all\ ages}} * YLD_{CANADA}^{all\ ages}\right) \Big/ population_i^{all\ ages}$$

Mortality based YLD averted are therefore calculated as:

(12)

$$mortality\ based\ YLD\ averted_i^{all\ ages} = mortality\ based\ YLL\ averted_i^{all\ ages} * \gamma - mortality\ based\ YLL\ averted_i^{all\ ages} * per\ capita\ YLD\ burden_i,$$

where the first term reflects the possible direct effects of expenditure in reducing morbidity (B in Table 1) and the second term captures the indirect effect of increases in morbidity due to increases in survival (C in Table 1).

The total DALYs averted due to a 1% change in health expenditure in each province is the sum of the survival effects (the YLL averted in (6), A in Table 1) and the net morbidity effects (YLD averted in (12), B-C in Table 1). This illustrates how estimates of mortality effects of health expenditure, in the form of elasticities, can be used to provide an indication of the likely survival (YLL averted) and morbidity effects (YLD averted). Although the elasticities applied to provincial data are for Canada as a whole, the health effects of a 1% change in provincial health expenditure will differ by province due to differences in the number observed deaths by age and gender and differences in age and gender specific conditional life expectancies. The amount of expenditure required to avert one DALY will also differ by province due to differences in total health expenditure.

(13) $$cost\ per\ DALY\ averted_i = \frac{1\% * government\ expenditure\ on\ health_i}{DALYs\ averted_i}$$

Nonetheless a number of assumptions have been required: i) that elasticities are similar across provinces; ii) that the estimates survival effects of changes in mortality are a good surrogate for morbidity effects; and iii) that the morbidity burden of disease is distributed across provinces in the same proportion as the survival burden of disease which can be calculated for each province.

DALY 2

The effect of changes in health expenditure on measures of survival burden of disease (YLL) can also be estimated directly from the cross country data (See Table 2). The estimated elasticity for YLL, ϵ^{YLL}, is only available at a national rather than provincial level. However, assuming that elasticities are similar across provinces this elasticity can be applied to province specific $YLL_i^{all\ ages}$ which are calculated from observed mortality and conditional life expectancies by age and gender (e.g., see (8) and (9)) above). Therefore, YLLs averted due to a 1% change in health expenditure can be directly estimated (14) rather than applying conditional life expectancies to estimates of deaths averted by age and gender (as required in (1) to (7) above).

(14) $$directly\ estimated\ YLL\ averted = 1\% * \left|\epsilon_{Canada}^{YLL}\right| * YLL_i^{all\ ages}$$

The possible direct and indirect effects on morbidity of changes in health expenditure which effects survival can be calculated in the same way as previously; assuming that that the estimated effects on survival can be used as a surrogate for likely effects on morbidity and with the indirect effect of increases in morbidity based on directly estimated survival effects. Therefore, the net morbidity effects are calculated in the same way as in (12) but with *directly estimated YLL$_i$ averted* replacing *mortality based YLL$_i$ averted* (E-C in Table 1).

DALY 3

As well as direct estimates of the effect on survival burden of disease, the effect of changes in health expenditure on measures of morbidity burden of disease (YLD) can also be estimated directly from the cross country data (See Table 2). DALY 3 uses direct estimates of the effect on survival burden in the same way as DALY 2 but combines these with direct estimates of the effect on morbidity. The estimated elasticity for YLD is only available at a national rather than provincial level. However, assuming that elasticities are similar across provinces this elasticity can be applied to province specific estimates of morbidity burden. Since province specific estimates of YLD are not available we assume that YLD are distributed across provinces in the same proportion as YLL as previously (11). The directly estimated YLD averted for a 1% change in provincial health expenditure is simply the product of the estimated YLD for that province and the estimated YLD elasticity for Canada (15).

(15) $$directly\ estimated\ YLD\ averted = 1\% * \left|\epsilon_{Canada}^{YLD}\right| * YLD_i^{all\ ages}$$

The total DALYs averted due to a 1% change in health expenditure in each province is the sum of the directly estimated survival effects (YLL averted in (14), D in Table 1) and the directly estimated morbidity effects (YLD averted in (15), F in Table 1).

DALY 4

The combined effect of changes in expenditure on survival and morbidity burden of disease (DALYs can also be estimated directly from the cross country data using country level estimates of DALY burden of disease (See Table 2). As for mortality, YLL and YLD the estimated elasticity for DALYs is only available at a national rather than provincial level but can be applied to province specific estimates of DALY burden assuming that the estimated elasticity is similar across provinces. Since province specific estimates of DALY burden are not available we assume, similar to previously, that DALY burden of disease is distributed across provinces in the same proportion as the survival burden of disease which can be calculated for each province (see (6), (7) and (11)). Therefore, a direct

estimate of DALYs averted for a 1% change in provincial health expenditure is simply the product of the estimated DALY burden for that province and the estimated elasticity for Canada (16).

(16) $$directly\ estimated\ DALY\ averted = 1\% * \left|\epsilon_{Canada}^{DALY}\right| * DALY_i^{all\ ages}$$

These 4 alternative ways to estimate health opportunity costs, as measured by the cost per DALY averted, make slightly different assumptions. One common one is that estimated elasticities, which are currently only available at a national level, can be applied equally across provinces. This might not be unreasonable since the differences in elasticities between countries are quite small based on Bokhari et al (2007), although this model only allows for two interaction terms which both have modest effects. The other common assumption is that the morbidity burden of disease, which is currently not available by province, is distributed across provinces in the same way measures of survival burden (YLL_i) which can be calculated at a provincial level. This might be reasonable for larger provinces which have similar epidemiology, but is less likely to be reasonable for smaller provinces which differ in the distribution of types of disease and its impact.

Nonetheless, the comparison of DALY 1 with DALY 4 does give some indication of whether it is reasonable to use estimates of the mortality effect of changes in health expenditure as a surrogate for likely survival and morbidity effects. This is particularly useful as other studies in high income countries have estimated elasticities for mortality outcomes using high quality within country data which overcomes some of the difficulties and challenges of estimation based on aggregate country level data. As a sensitivity analysis we apply two different all-cause mortality elasticities estimated for the UK (Claxton et al 2017 and Andrews et al 2017) in place of the mortality elasticities based on Bokhari et al to re-calculate cost per DALY averted for DALY 1.

3. Results

Estimated elasticities for Canada

The extended Bokhari et al. (2007) model generated country-specific elasticities for all of the countries in the model (n=127). Elasticities only differed between countries due interactions with level of infrastructure and shocks in donor funding. The elasticities for Canada for each of the six measures of health outcome are reported in Table 2 along with the average elasticities of all 25 high income countries (HICs) in the dataset.[1]

[1] Countries included: Australia, Austria, Canada, Chile, Croatia, Estonia, Finland, France, Germany, Hungary, Italy, Japan, Lithuania, Netherlands, New Zealand, Portugal, Singapore, South Korea, Spain, Sweden, Switzerland, Trinidad and Tobago, United Kingdom, United States and Uruguay. St Kitts and Nevis is also excluded for the sake of comparison across outcomes due to its missing outcome data for DALY, YLL and YLD models.

Table 2. Estimated elasticities for Canada

Mortality (deaths per 1,000)	Canada	Average for high income countries
Children under-5	-0.3412	-0.3549
Adults females	-0.1924	-0.1944
Adult males	-0.1928	-0.2000
DALYs	-0.2137	-0.1929
YLLs	-0.3032	-0.2765
YLDs	-0.0294	-0.0246

The elasticities for Canada are comparable to the mean of estimates for other HICs. Among HICs very few receive donor funding, which means that the primary driver of differences in estimated elasticities is due to the interaction term combining spending and level of infrastructure (proxied by 'paved roads per unit of area'). Canada has a very low value for this variable, due to the sparsity of its population, and so this is almost entirely responsible for why there are small differences between Canada's estimated elasticities and the average for all HICs.

Cost per DALY averted

The estimates of cost per DALY averted for Canada as a whole and for each province are reported in Table 3 and are also expressed as a % of provincial GDP per capita.

The estimates of cost per DALY for Canada as a whole are not the average of the cost per DALY ratios across the provinces but the ratio of the sum of changes in expenditure to the sum of DALYs averted across the provinces. The cost per DALY for Canada as a whole is similar using DALY 1 and DALY 4 which does give some indication that it might be reasonable to use estimates of the mortality effect of changes in health expenditure as a surrogate for likely survival and morbidity effects. This is also reflected in the results by province where DALY 1 and DALY 4 tend to provide relatively similar estimates, with the exception of two provinces (Prince Edward Island and Yukon).

DALY 2 consistently provides the lowest cost per DALY for Canada as a whole and across the provinces. This reflects the fact that the estimated elasticity for survival effects (YLL) is greater in magnitude than for adult mortality (see Table 2). This larger, directly estimated, effect on survival (YLL averted) is then used as a surrogate for morbidity effects. However, DALY 3 consistently provides the highest cost per DALY estimate for Canada and for each of the provinces. This reflects fewer DALYs averted due to the much lower magnitude of the estimated elasticity for morbidity effects (YLD, see Table 3), i.e., the smaller effect on morbidity more than offsets the larger effect on survival compared to DALY 1 (with the exception of Yukon). Although these differences and the differences in the elasticities reported in Table 2 might indicate that mortality effects underestimate survival effects in adult populations and that both mortality and survival effects may overestimate morbidity effects, this should not be over-interpreted as the estimated elasticities are not based on Canadian within country data but country level data with limited interactions for country level effects. However, in general the comparison of DALY 1 and DALY 4 does suggest that using estimates of the mortality effect of changes in health expenditure as a surrogate for likely survival and morbidity effects may not be unreasonable albeit with additional uncertainty.

Table 3. Cost per DALY averted and as a percent of GDP per capita by province

	Cost per DALY averted (2013 C$)			
	DALY 1	DALY 2	DALY 3	DALY 4
Canada	$97,321	$66,661	$113,681	$89,334
	180%	123%	211%	165%
Alberta	$125,997	$87,175	$149,636	$117,589
	147%	102%	175%	137%
British Columbia	$96,042	$64,335	$109,752	$86,247
	193%	129%	220%	173%
Manitoba	$104,498	$72,502	$122,729	$96,444
	212%	147%	249%	196%
New Brunswick	$90,166	$60,247	$101,819	$80,013
	214%	143%	242%	190%
Newfoundland and Labrador	$104,902	$70,603	$119,022	$93,531
	161%	108%	182%	143%
Northwest Territories	$249,536	$175,519	$298,690	$234,720
	248%	175%	297%	234%
Nova Scotia	$89,814	$60,108	$101,360	$79,652
	219%	147%	248%	195%
Nunavut	$177,375	$142,492	$236,380	$185,755
	282%	226%	376%	295%
Ontario	$95,706	$65,573	$112,111	$88,101
	187%	128%	219%	172%
Prince Edward Island	$82,939	$54,791	$91,618	$71,997
	212%	140%	234%	184%
Quebec	$87,446	$60,013	$102,159	$80,280
	196%	134%	228%	180%
Saskatchewan	$99,467	$69,497	$117,491	$92,328
	132%	92%	156%	123%
Yukon	$155,899	$102,780	$173,830	$136,601
	217%	143%	242%	190%

The four alternative ways to calculate cost per DALY averted provide quite similar estimates across most provinces. To some extent this might be expected as it is assumed that estimated elasticities, which are currently only available at a national level, can be applied equally across provinces. Insofar as provinces have similar health expenditure per capita and similar mortality rates, conditional life expectancies and population distribution, the cost per DALY averted will inevitably be very similar. This also explains why the cost per DALY averted differs for some of the smaller provinces where per capital heath expenditure is higher and where the population, mortality rates and conditional life expectancies differ from the larger provinces (e.g., Yukon, Northwest Territories and Nunavut).

Figure 1 illustrates the range of estimates for Canada and for each province by under-5 mortality rate. The average of the range of values for each province is not the average for the four cost per DALY ratios but the ratio of a 1% change in expenditure to the average DALYs averted across these

four estimates. Few strong patterns emerge but it is clear that the epidemiology of Nunavut and to some extent Northwest Territories is quite different to the other provinces. The high under-5 mortality in Nunavut would, other things equal tend to reduce the cost per DALY averted. However, this is more than offset by the higher per capita health expenditure and lower conditional life expectancies.

Figure 1. Cost per DALY averted by under-5 mortality rate

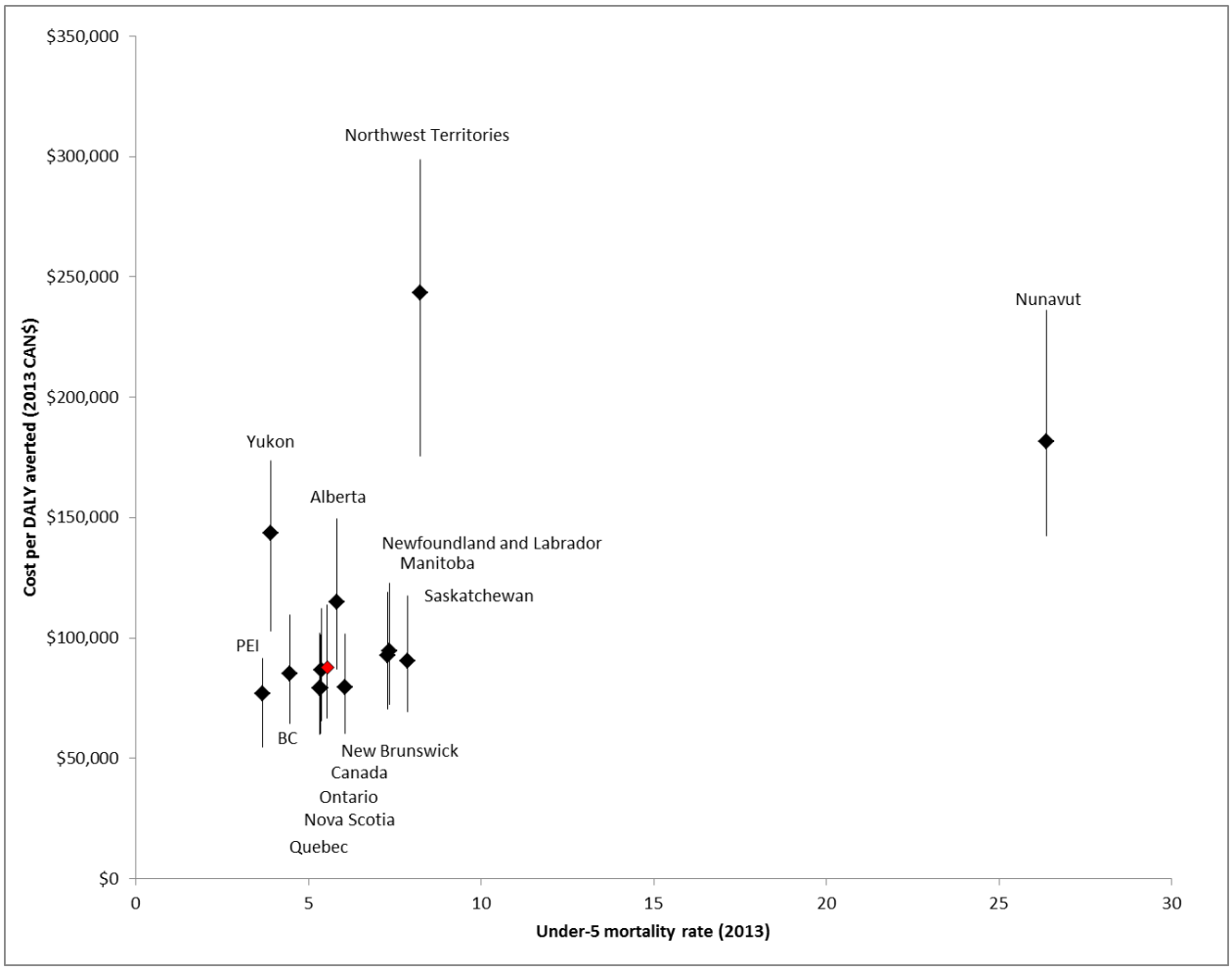
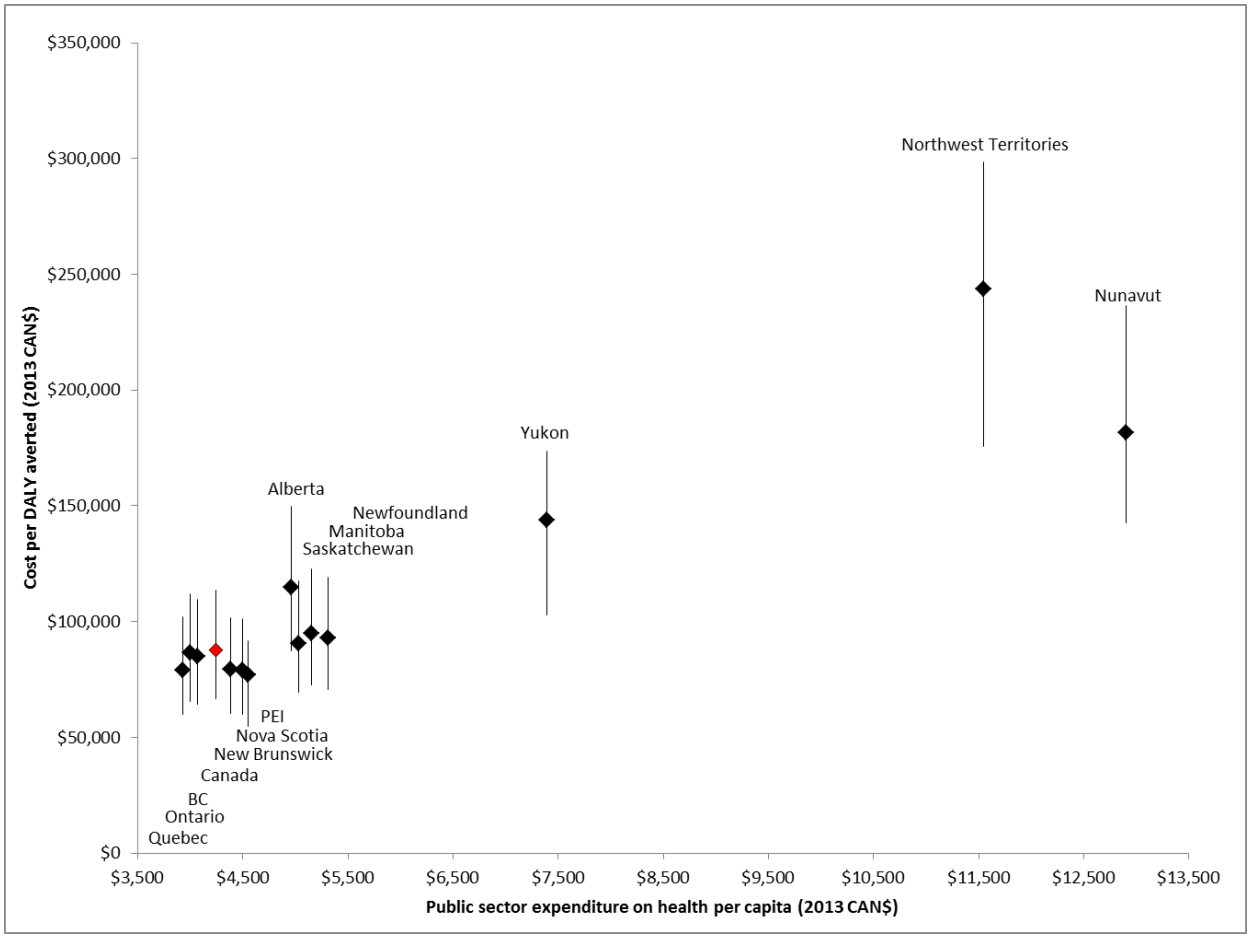


Figure 2 illustrates the same cost per DALY averted estimates but now by per capita public expenditure on health. It suggests that the cost per DALY averted increases with per capita health expenditure which is, in general, what might be expected, although this is to some extent inevitable given the methods used to generate these estimates. It also illustrates the similarity in the range of estimates for most provinces but also why others (Yukon, Northwest Territories and Nunavut) differ. The apparent similarity in the range of cost per DALY averted between most provinces should not be over interpreted as estimates would also be expected to differ if provinces are able to generate health at different rates, which would be reflected in differing elasticities. This underscores the importance of further research to estimate these values at the provincial level in Canada using within country and within province data.

Figure 2. Cost per DALY averted by per capita public expenditure on health



Sensitivity analysis

Table 4 reports the cost per DALY averted (DALY 1) for Canada and by province using all-cause mortality elasticities from Claxton et al. (2017) and Andrews et al. (2017), which are applied equally to under-5 and adult mortality. Claxton et al (2017) estimated mortality elasticities by disease area, which were combined with mortality data to produce an implied all-cause mortality elasticity estimate of -1.0278 for 2012/13 expenditure data and 2012/13 to 2014/15 mortality data. Andrews et al (2017) used an alternative approach to identification but applied it to total expenditure and mortality outcomes to directly estimate an all-cause mortality elasticity of -0.705 for 2005/06. The important differences between Claxton et al (2017) and Andrews et al (2017) are the year of analysis, the approach to identification and the level of aggregation. Recent work reported in Claxton et al (2017) does not suggest strong trends in implied all cause elasticities over the previous 10 years of expenditure data, i.e., assuming elasticities to be stable over time is not unreasonable. On-going work also suggests that the two approaches to identification (when applied at disease area level) generate similar cost per QALY estimates for the UK.

Although differences in estimated elasticities and cost per QALY based on these approaches are not statistically significant, in general direct estimates of all cause elasticities tend to be lower than those implied by estimates at disease area level. This is to be expected as all cause estimates will be subject to some aggregation bias compared to those which are able to capture any heterogeneity of effect by disease area. Both estimates are higher in magnitude than the mortality elasticity

estimates from the extended Bokhari et al (2007) model. Again, this might be expected given the greater dangers of aggregation bias using country level data and the difficulty of fully accounting for unobserved heterogeneity and endogeneity using the instruments for health expenditure that are available across countries. These differences in estimated all cause elasticities are reflected in the cost per DALY averted with the lowest associated with Claxton et al (2017) and the highest with Bokhari et al (2007).

Table 4. Cost per DALY averted based on alternative estimates of mortality effects

	Cost per DALY averted for DALY 1 (2013 C$)		
	Claxton et al (2017)	Andrews et al (2017)	Bokhari et al (2007)
Canada	$19,914	$29,032	$97,321
Alberta	$26,060	$37,991	$125,997
British Columbia	$19,227	$28,029	$96,042
Manitoba	$21,722	$31,667	$104,498
New Brunswick	$18,265	$26,628	$90,166
Newfoundland and Labrador	$21,392	$31,186	$104,902
Northwest Territories	$52,191	$76,087	$249,536
Nova Scotia	$18,002	$26,244	$89,814
Nunavut	$41,776	$60,903	$177,375
Ontario	$19,606	$28,582	$95,706
Prince Edward Island	$16,425	$23,945	$82,939
Quebec	$17,936	$26,147	$87,446
Saskatchewan	$20,804	$30,329	$99,467
Yukon	$30,633	$44,659	$155,899

Setting aside the three provinces which have especially high per capita public health expenditure (Yukon, Northwest Territories and Nunavut) the range of potential cost per DALY averted for Canada and for the other provinces is in the region of $20,000 to $100,000 per DALY averted. The lower part of this range is consistent with the implied cost per QALY gained for Canada based on the analysis in Woods et al 2016 ($25,292 to $31,915 in 2013 US$). The relatively modest difference between the remaining provinces follows the same pattern as seen previously in Table 3 and Figure 1 and 2. However, as discussed above, these apparent similarities should not be over-interpreted as the estimated elasticities are applied equally across provinces. Insofar as provinces have similar health expenditure per capita and similar mortality rates, conditional life expectancies and population distribution, then the cost per DALY averted will inevitably be very similar. These considerations and the wide range of potential estimates of cost per DALY averted using currently available estimates in Table 4 indicates the importance of further research to provide province specific elasticity estimates for Canada using within country and within province data.

4. Discussion

Estimates of the health opportunity costs of additional health care expenditure are critical for informing assessments of whether the improvement in health outcomes offered by investing additional resources in a new health technology exceeds the improvement in health that would have been possible if the additional resources required had, instead, been made available for other health care activities. Commonly established implied norms, such as 1-3x GDP per capita, are often inappropriately applied in practice to judge cost-effectiveness (Bertram et al. 2016). Such values generally reflect the social demand for health (i.e., a view of what value ought to be placed on improvements in health) rather than an evidence based assessment of health opportunity costs given actual levels of expenditure. As such, they do not reflect the health that the HCS is currently able to deliver with the resources available, i.e., the 'supply side' of the HCS. Adopting 'thresholds' to judge costs effectiveness which are too high and do not reflect the 'supply side' will lead to decisions that reduce overall health because the health gained from adopting a new technology will be more than offset by the health opportunity costs elsewhere in the HCS. It will also mean that the HCS will pay too much for the benefits offered by new branded pharmaceuticals because the additional cost of patented innovations will do more harm than good for population health during the remaining patent period. As well as leading to net harms for population health it may also exacerbate health inequalities and unwarranted variations in access to other health care, depending on where the health opportunity costs of additional health care costs tend to fall.

The framework of analysis set out in this report illustrates how estimates of the relationship between mortality and variations in health care expenditure can be employed alongside province specific data on demography, epidemiologic profile and expenditure to inform estimates of health opportunity costs. While data is readily available for the latter, reliable estimates of the relationship between mortality and variations in health care expenditure present a challenge.

This report employed estimates estimated using the model used by Bokhari et al (2007), which applies an instrumental variable method to cross-sectional data, and models both public expenditure on health and a country's GDP as endogenous variables. While Bokhari et al. (2007) find a statistically and economically significant effect of public expenditure on health reducing mortality outcomes, there is no clear and consistent finding in the literature that evaluates the relationship between mortality and variations in health care expenditure using country level data (Gallet & Doucouliagos 2017). This is often driven by the methodological approach adopted by each study, addressing the considerable challenges including the important country-level heterogeneity, much of which is unobserved and controlled for using existing data, even if it is assumed that systematically unbiased measurements are available. Estimates of mortality elasticities based on country level data tend to be lower than those based on within country data which are likely to reflect the greater dangers of aggregation bias using country level data and the difficulty of fully accounting for unobserved heterogeneity and endogeneity using the instruments for health expenditure that are available across countries.

The framework of analysis employed here can be applied to the results of any econometric study which is thought to identify plausible effects on mortality of changes or differences in health expenditure. Other within-country studies have estimated the marginal productivity of health expenditure in producing health (QALYs) (Martin et al. 2008; Claxton, Martin, et al. 2015; Edney et

al. 2017; Vallejo-Torres et al. 2016). A sensitivity analysis was conducted based on recent work in the UK, where all-cause mortality elasticity estimates have been estimated using an instrumental variable approach with different devolved health care bodies as the unit of observation providing the variation in expenditures, outcomes and health care need variables. The implied all-cause mortality elasticity estimate, -1.0278, found by Claxton et al (2017) is considerably higher in magnitude to any of the mortality elasticity estimates from the extended Bokhari et al (2007) model. Another study, Andrews et al (2017) used an alternative approach to identification to directly estimate an all-cause mortality elasticity estimate for the UK NHS of -0.705. Once again, this is higher than the results from Bokhari et al (2007). Using these two elasticities (-1.0278 and -0.705) as inputs for the calculation of the DALYs averted from a 1% change in expenditure results in a considerably lower estimates of the cost per DALY averted for Canada ($19,914 and $29,032 respectively) and for the provinces (see Table 4).

These estimates are from within-country studies of the relationship between health and expenditures, set in the context of the UK, which form part of a growing literature of studies of this kind. Edney et al (2017) and Vallejo-Torres et al (2016) perform similar studies in the contexts of Australia and Spain. The overall results in terms of expenditure per QALY give similar results to these UK studies, but the elasticities cannot be directly compared. In the case of Edney et al. (2017), an elasticity, -1.602, is estimated on HRQoL-weighted YLL reflecting the percentage change in QALYs resulting from delayed mortality for a given percentage increase in expenditure. Vallejo-Torres et al. (2016) instead estimate an elasticity, -0.0681, reflecting the percentage effect on Quality Adjusted Life Expectancy (QALE) that results from a given percentage increase in expenditure in a given year, which would then need to be sustained over the lifetime period (Lichtenberg 2004).

Previous work has estimated cost per DALY averted for 123 low- and middle-income countries based on elasticities estimated from the Bokhari et al (2007) model but using country level data on health expenditure, epidemiology and demographics from the Global Burden of Disease database and the World Bank (Ochalek et al. 2015). Using these sources, which have been standardised to be internationally comparable, rather than Canadian data would have resulted in slightly higher estimates of the DALYs averted from health expenditure so slightly lower cost per DALY averted estimates ($53,048 to $89,827 per DALY averted rather than $66,661 to $113,681 using Canadian data in Table 3). However, it is the larger differences due to alternative but plausible effects on mortality of changes in health expenditure illustrated in Table 4 which indicate the importance of further research to provide province specific elasticity estimates for Canada using within country and within province data.

5. Recommendations

The range of potential cost per DALY averted for Canada and for most provinces is in the region of $20,000 to $100,000 per DALY averted in Table 4, with the lower estimates associated with more recent work using within country rather than country level data. Given the greater dangers of aggregation bias of using country level data and the difficulty of fully accounting for unobserved heterogeneity and endogeneity using the instruments for health expenditure that are available across countries, it is the lower end of this range that might be regarded as more plausible. An assessment that elasticities using within country data for Canada are likely to be higher than those based on country level data is plausible and tends to be supported by growing literature from other countries.

A cost per DALY threshold is likely to be less than $50,000 for Canada as a whole and is likely to be similar across most provinces.

A measure of heath benefit more appropriate to Canada would be QALY gained rather than DALYs averted. However, currently there are no estimates of QALY burden of disease which would allow estimates of the mortality effects of changes in expenditure to be used to estimate a cost per QALY threshold.

Nonetheless, estimates of cost per DALY averted and costs per QALY gained of changes in expenditure are likely to be similar. Although there will be important differences between the same effects measured as QALYs gained or DALYs averted in particular diseases (due to differences in health state descriptions and weights attached to disability and quality of life) (Robberstad 2009), these are not systematic so DALY and QALY effects on average across all disease areas are unlikely to differ markedly. Importantly the type of age related weights previously used in calculating DALYs, which would lead to more systematic differences have not been used. However, one aspect of how DALYs averted are calculated does suggest that (other things equal) DALYs averted will then to underestimate QALY gains. This because reductions in mortality and increases in survival changes conditional life expectancies so increases the burden of disease as measured by DALYs (Airoldi & Morton 2009).

A cost per QALY threshold is likely to be similar or lower than a cost per DALY averted threshold

This is also consistent with the range of implied cost per QALY gained for Canada based on the analysis in Woods et al 2016 ($26,596 - 33,560 in 2013 CAN), which extrapolates the UK findings based on estimates of the income elasticity of demand for health and assumptions about the relative underfunding of HCS (i.e., the shadow price for public expenditure on health). Estimates based on this analysis have been adopted in Norway while further research using within country data are explored. Using the approach taken by Norway (assuming and income elasticity of one) would provide a cost per QALY threshold for Canada of $28,089.

A cost per QALY threshold of $30,000 per QALY would be a reasonable assessment of the health effects of changes in health expenditure for Canada as a whole and is likely to be similar across most provinces.

The currently available estimates of the effect of changes in health expenditure on mortality outcomes have focused on the effects of changes in public rather than private expenditure. The

estimates for Canada applied these estimated elasticities to public expenditure (federal and provincial). Applying the same elasticities to total expenditure (including private expenditure) would not change the estimates of cost per DALY averted. However, if estimated elasticities of public and private expenditure differ, then the cost per QALY gained or cost per DALY averted of changes in public and private expenditure would also differ, e.g., if the marginal productivity of private expenditure is lower than public expenditure the cost per QALY threshold for changes in private expenditure will be higher. However, in the absence of evidence of differences in the marginal productivity of public and private health expenditure adopting the same cost per QALY threshold for both categories of expenditure would not be unreasonable. Adopting a threshold to that reflects health opportunity costs of public health expenditure will ensure that prices of new pharmaceuticals do not undermine health outcomes of publically funded health care.

6. Further research

Further research to provide Canadian and/or province specific elasticity estimates using within country and within province data should be regarded as a priority. Improving estimates of health opportunity costs for the Canadian provinces could focus on the following issues: i) estimating mortality elasticities for Canada as a whole or for each of the provinces using within country data; ii) developing estimates of QALY rather than DALY burden of disease that are province specific and iii) directly estimating the effect of changes in health expenditure on QALY outcomes for each province.

Estimating mortality elasticities for Canada using within country data

Estimates of an all cause mortality elasticity for Canada as a whole could exploit cross sectional variation in expenditure and outcomes, seeking potential instruments from socioeconomic variables and/or exogenous elements in how funding tends to be allocated, following Claxton et al (2017) and Andrews et al (2017) respectively. This would start to identify where in the $20,000 to $100,000 range might be most plausible. However, it would still require that a single elasticity estimated at a national level be applied equally across all provinces. It would also mean that differences between provinces would be modest and may not reflect real differences in the marginal productivity for health care expenditure, i.e., insofar as provinces have similar health expenditure per capita and similar mortality rates, conditional life expectancies and population distribution, then the cost per DALY or QALY estimates will also be very similar. This could be relaxed by attempting to estimate all cause elasticities for each province. This might be possible using interaction terms for province when estimating a national all cause model or estimating separate province specific all cause models. The latter poses the challenge of finding units of analysis with sufficient variation in expenditure and outcomes within province as well as suitable instruments.

However, in general, direct estimates of all cause elasticities tend to be lower than those implied by estimates at disease area level because they are likely to be subject to some aggregation bias compared to those which are able to capture any heterogeneity of effect by disease area. Therefore, it would be an advantage to estimate elasticities (national and provincial) by disease areas. However this would require expenditure by disease area as well as mortality outcomes to be available at the unit of analysis that will provide sufficient variation. Nonetheless estimates of all cause elasticities for Canada and/or the provinces based on within country data would be a

significant improvement over existing estimates, whether or not they are directly estimated or implied by estimates at disease area level.

Province specific estimates of QALY burden of disease

The analysis above applies estimated all cause elasticities to measures of burden of disease by province. The survival burden of disease is province specific; using data on deaths by age and gender and conditional life expectancies for each province. However, measures of morbidity burden of disease are not routinely available, so a measures of morbidity for Canada as a whole have been used (YLD) from the Global Burden of Disease data base. This poses two difficulties. Province specific estimates of YLD are not available so it is assumed that YLD are distributed across provinces in the same way as survival burden (YLL_i) i.e., assuming that the morbidity burden of disease is likely to be higher (lower) where the survival burden is higher (lower). The second problem is that the measure of health effect of changes in expenditure is expressed using the measures of disease burden that are currently available, i.e., DALY averted (DALY = YLL+YLD) rather than QALYs, which would be more appropriate to decision making processes in Canada because it is more likely to reflect the dimensions of quality of life and preferences for health states relevant to Canada (Airoldi & Morton 2009; Robberstad 2009).

The QALY effects of changes in expenditure could be estimated from mortality elasticities based on measures of the QALY burden of disease across provinces. This would require age and gender quality of life norms and decrements in quality of life due to disease. It would also require estimates of the incidence and duration of disease, as well as mortality and conditional life expectancies. This was the approach taken in the UK which estimated QALY burden of disease for all 3 digit ICD codes (Claxton et al 2015). However, this work estimated elasticities by disease area which were then applied to QALY burden in each disease area rather than applying an all cause elasticity to a measure of the total QALY burden of disease.

Estimating the effect of changes in health expenditure on QALY outcomes for each province

Measures of QALY burden of disease for each province would overcome some difficulties and allow results to be expressed as cost per QALY gained rather than DALY averted. However, such cost per QALY estimates would still require an assumption that estimates of the mortality effects of changes in expenditure are a good surrogate for a more complete measure of the health effects which include survival and quality of life.

The similarities between estimates based on DALY 1 and DALY 4 for Canada as a whole and for most provinces in Table 3 does give some indication that it might be reasonable to use estimates of the mortality effect of changes in health expenditure as a surrogate for likely survival and morbidity effects. Estimates in the UK are founded on similar assumptions since quality of life outcomes by disease and geographic areas are not available to directly estimate them. More recently these assumptions have been examined by conducting a formal quantitative elicitation exercise with UK clinical experts in the key disease areas. The results of this expert elicitation suggest that the assumptions required are not unreasonable and, if anything, are likely to underestimate the effects of changes in health expenditure in the UK (Soares et al. 2018).

Therefore, Canada could rely on similar assumptions and focus efforts on estimating mortality based elasticities, ideally by province, if possible by disease area, combined with measures of QALY rather than DALY burden of disease. A similar approach to elicitation could be conducted with clinical experts from Canada focusing on key disease areas relevant to each province. Alternatively, attempts could be made to directly estimate the effects of changes in expenditure on quality of life outcomes. There are no examples of where that has been done by disease area, but other studies have been able to estimate the effect on mortality and survival separately from effect on quality of life outcomes (Edney et al. 2017) or directly estimate the effect on changes in quality adjusted life expectancy, which in principle captures both effects (Vallejo-Torres et al. 2016). Direct estimation of QALY effects by province would be ambitious and would require careful consideration of whether the type of quality of life data, at the unit of observation available, would offer sufficient variation. Although the combination of cross sectional and time series data does offer more opportunities for estimation, the high persistence often found in these data, especially in the UK, may mean that it is variation in the cross sectional data that is likely to be most important.

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Appendix A. Variables used to calculate DALYs averted

Variable	Measure used	Source	Year used
1-year probability of death for females, males and both for ages in a given five-year age category (n-n+4)	Where life table data is given by 1-year age group: $P(annual\ mortality\ n\ to\ n+4) = 1 - \left(\prod_{t=n}^{n+4}(1-p_t)\right)^{\frac{1}{5}}$ Where life table data is given by 5-year age group: $P(annual\ mortality\ n\ to\ n+4) = 1 - (1-p_{n\ to\ n+4})^{\frac{1}{5}}$	Statistics Canada. 2017. Life tables, Canada, provinces and territories, catalogue no. 84-537-X. http://www.statcan.gc.ca/pub/84-537-x/84-537-x2017001-eng.htm	2011-2013
Absolute number of death for females, males and by five-year age category (n-n+4)	$Absolute\ deaths\ n\ to\ n+4 = P(annual\ mortality\ n\ to\ n+4) * population\ n\ to\ n+4$	Calculated variables from life tables.	
Conditional life expectancy for females, males and both by five-year age category (n-n+4)	e_x by 5-year age category 0-90+. Where e_x given by year e_x for lowest age in category used. Where e_x given for over 90 e_x at 90 used.	Statistics Canada. 2017. Life tables, Canada, provinces and territories, catalogue no. 84-537-X. http://www.statcan.gc.ca/pub/84-537-x/84-537-x2017001-eng.htm e_x given by year (0-110+) for all provinces except Prince Edward Island, Nunavut, Northwest Territories and Yukon.	
Population by females, males and both by five-year age category (n-n+4)	Population by 5-year age category 0-100+.	Statistics Canada. Table 051-0001 - Estimates of population, by 5-year age group 0-100+) and sex for July 1, Canada, provinces and territories, annual (persons unless otherwise). CANSIM: http://www5.statcan.gc.ca/cansim/a26?id=510001	2013

Per capita GDP expenditure based at current prices ($' 000)	GDP expenditure based / Total Population	GDP: Statistics Canada, CANSIM, table 384-0038. Total Population: Statistics Canada, CANSIM, table 051-0001.	2013
Public sector expenditure on health (provincial government; federal direct; municipal government; social security funds)	Total value, current dollars	National Health Expenditure Database, 1975 to 2016, Canadian Institute for Health Information. Excel Sheet: nhex-Series-D3-2016_en.xlsx https://www.cihi.ca/en/national-health-expenditure-trends	2013