

Reimbursement of Drugs for Rare Diseases in Canada: Do Treatment Cost and Cost-effectiveness Ratio Correlate with Epidemiologic Factors?



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Maity T,¹ Mann K,² Mott PJ,² Quader T,² Malmberg C²¹ Health Policy and Management, DeGroote School of Business, McMaster University, Hamilton, Canada² EVERSANA Canada Inc., Burlington, Canada

INTRODUCTION

In Canada, rare diseases are considered life-threatening, debilitating, or serious and chronic conditions that affect <50 individuals per 100,000 population [1]. Pharmaceutical treatments for these diseases are known as drugs for rare diseases (DRDs or “orphan drugs”), which often have high treatment costs that are needed to offset the high drug development investment for a small group of potential patients. The high costs of DRDs also typically contribute to high incremental cost-effectiveness ratios (ICERs) that exceed conventional willingness to pay thresholds (e.g., \$50,000/quality-adjusted life year [QALY]). While most health economists agree that it is inappropriate to apply the same ICER thresholds to DRDs and non-DRDs, there is less agreement regarding what values should be applied for DRDs during health technology assessment (HTA).

Unlike many developed countries, Canada does not have a comprehensive framework for regulatory review or reimbursement of DRDs [1-4], and the Canadian Agency for Drugs and Technologies in Health (CADTH) has not expressed an official position on acceptable price and ICER value for DRDs. These factors have created uncertainty when DRD manufacturers seek public reimbursement in the Canadian market, which may contribute to Canadians only having publicly funded access to approximately 60% of globally marketed DRDs [5,6]. Nevertheless, we have observed that sponsors have received favorable recommendations from CADTH for DRDs despite high sponsor-submitted values for annual costs and/or ICERs. Therefore, we aimed to better understand the economic values that have been presented to CADTH in successful Canadian DRD submissions.

- **Primary objective:** to evaluate whether annual drug costs and/or ICERs for DRDs were correlated with the size of the eligible patient population.
- **Secondary objective:** to evaluate whether DRDs indicated for only children had higher annual drug costs and/or ICERs (vs. DRDs indicated for only adults).

METHODS

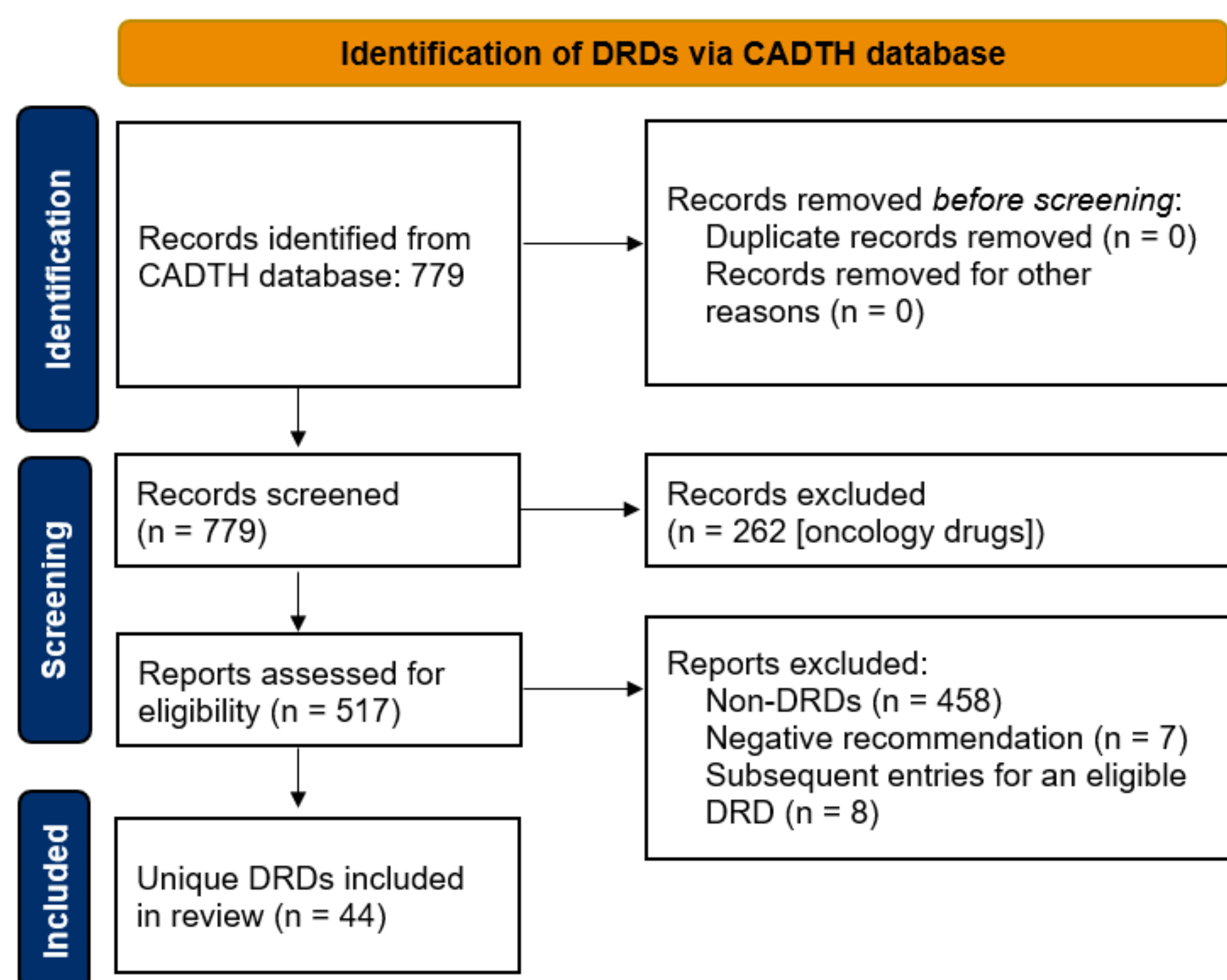
Inclusion and Exclusion Criteria

We defined DRDs as drugs for non-oncology diseases with a prevalence of <50/100,000 population. Oncology drugs were excluded because rarity does not drive pricing in oncology indications [7]. Only DRDs with positive CADTH recommendations (“reimburse” or “reimburse with conditions”) were included because clinical benefit is the first criterion in CADTH’s deliberative framework. Only the first indication reviewed by CADTH was used for DRDs with multiple indications (Figure 1).

Data Extraction and Analyses

Published CADTH recommendations were used to extract data regarding disease prevalence, the indicated age group (children and/or adults), and sponsor-submitted values for annual per-patient drug costs and ICERs (based on public list prices). Prevalences were categorized into subgroups as <2, 2 to <25, and ≥25 cases/100,000 population; incidence rates were not used because of sporadic reporting. Median/mean estimates of costs and ICERs were calculated within each prevalence subgroup, and their correlations with disease rarity were analyzed using R.

Figure 1. DRD selection flowchart.



RESULTS

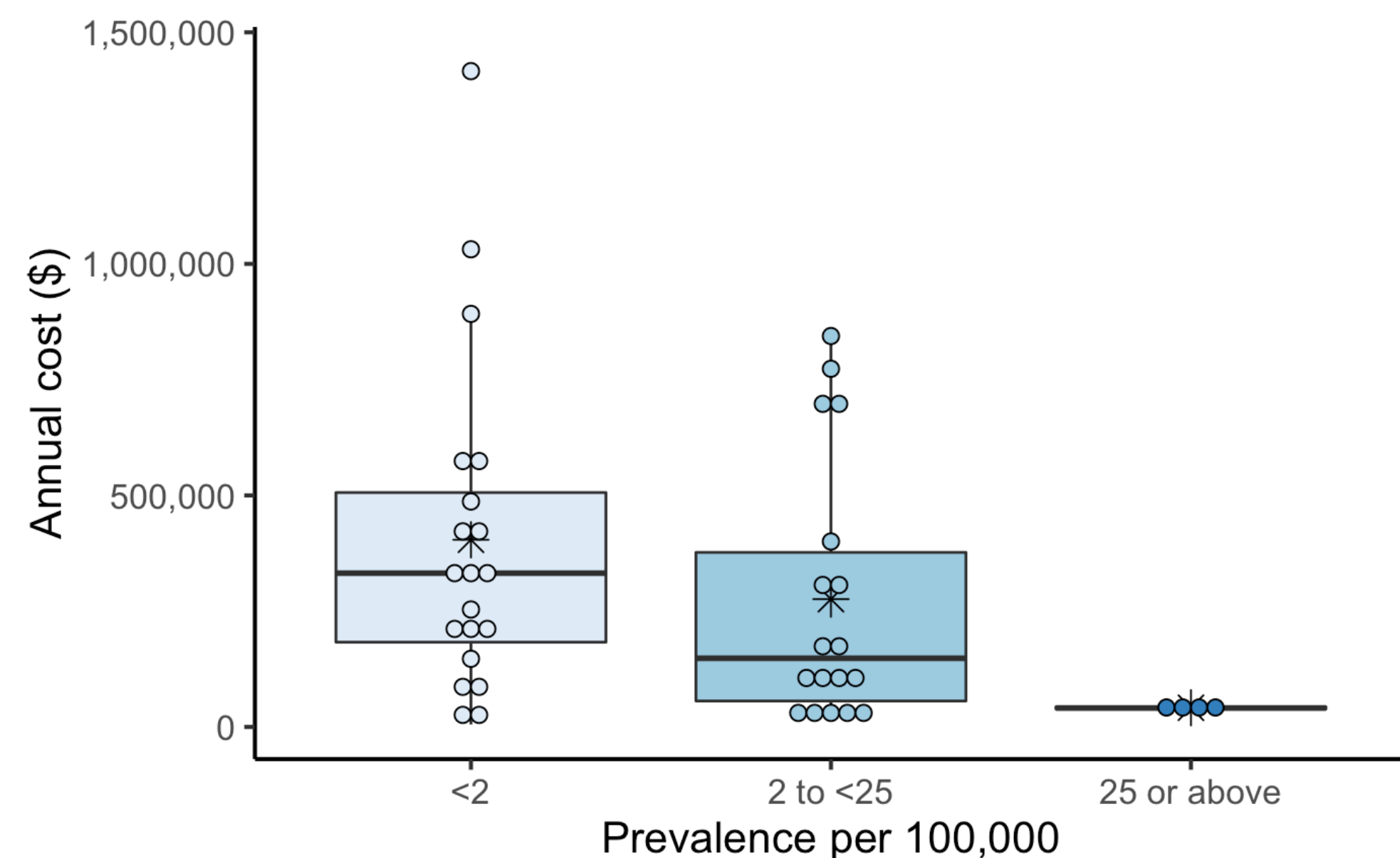
Characteristics of Included DRDs

Among 59 non-oncology DRDs reviewed by CADTH during 2012-2022, we included 44 unique DRDs with a positive CADTH recommendation. The included DRDs were categorized according to prevalence as <2 (24 DRDs), 2 to <25 (16 DRDs), and ≥25 cases/100,000 (4 DRDs). Other characteristics of the included DRDs are below.

- Prevalence range: 0.0019 to 44.7 cases/100,000 population
- Age groups: 17 DRDs for adults and children, 7 DRDs for only children, and 20 DRDs for only adults
- Annual sponsor-submitted per-patient cost range: CAD\$5,358/year to CAD\$1,416,168/year
- Annual sponsor-submitted ICER range: CAD\$46,160/QALY to CAD\$4,485,000/QALY

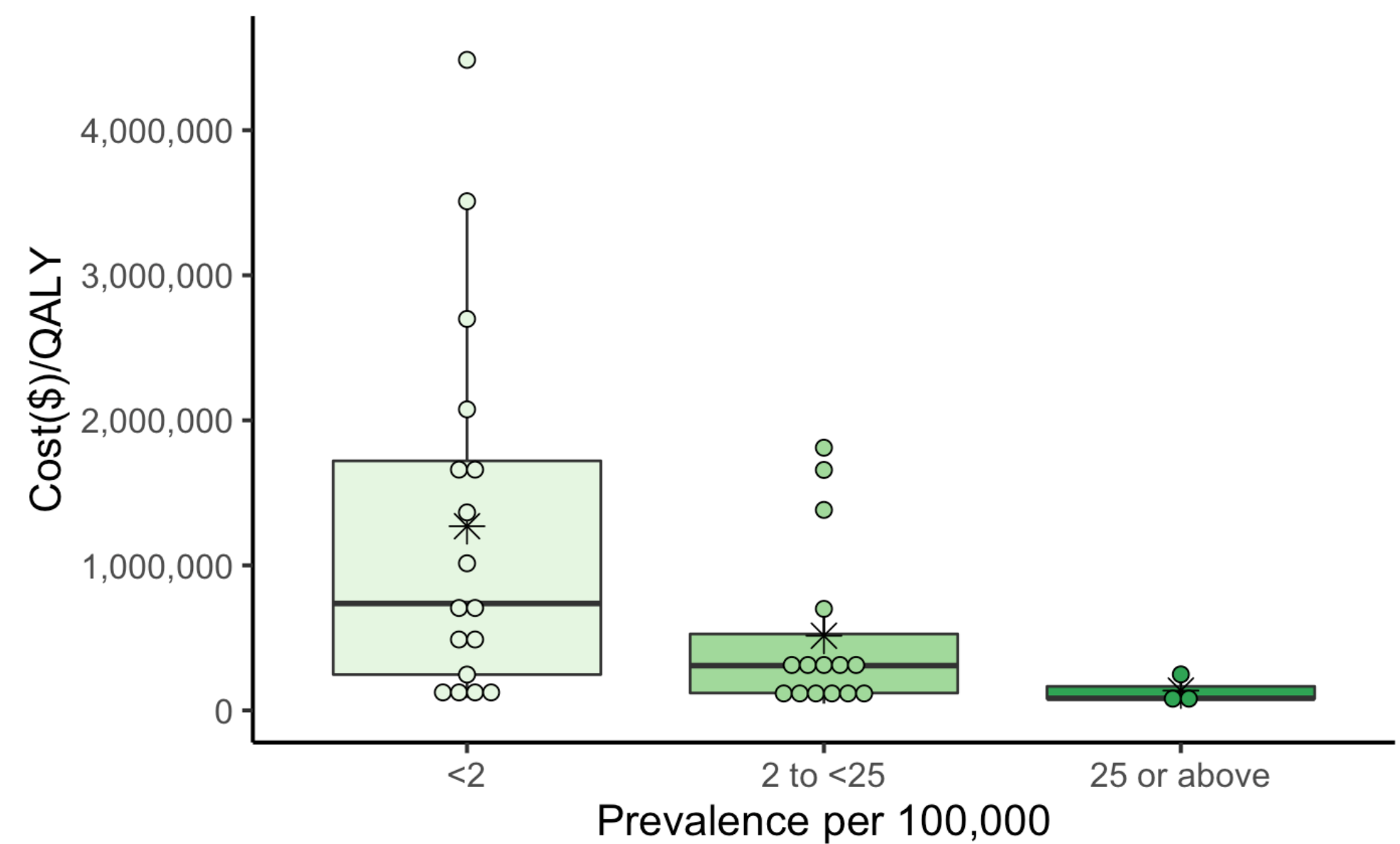
Among DRDs with positive CADTH recommendations, the average annual per-patient costs increased as the size of the patient population decreased (Figure 2). For every 10-fold decrease in disease prevalence, there was an approximately **CAD\$211,000** increase in annual per-patient cost.

Figure 2. Annual Per-patient Costs of DRDs According to Disease Prevalence Category.



Among DRDs with positive CADTH recommendations, the average ICERs also increased as the size of the patient population decreased (Figure 3). For every 10-fold decrease in disease prevalence, there was an approximately **CAD\$666,000** increase in the average ICER.

Figure 3. Average ICERs of DRDs According to Disease Prevalence Category.



In addition to annual costs and ICERs increasing with disease rarity, we observed even higher values for the 7 DRDs that were indicated for only children (Table 1). The average annual per-patient cost of DRDs for only children was approximately 2-fold greater than the average per-patient cost of DRDs for only adults. Similarly, the average ICER of DRDs for only children was approximately 3.5-fold greater than the average ICER of DRDs for only adults.

Table 1. Annual Costs and ICERs According to Indicated Age Category.

Prevalence category	Only children	Only adults	Adults & children	Average (all DRDs)
Average annual per-patient costs (CAD\$/year)				
Subgroup totals	\$580,338	\$285,603	\$233,093	\$314,722
<2 cases/100k	\$724,405	\$382,817	\$265,661	\$404,273
2 to <25 cases/100k	\$388,248	\$314,012	\$200,525	\$275,946
≥25 cases/100k	–	\$41,457	–	\$41,457
Average ICERs (CAD\$/QALY)				
Subgroup totals	\$1,549,748	\$439,409	\$944,890	\$849,227
<2 cases/100k	\$2,158,454	\$546,731	\$1,521,550	\$1,270,014
2 to <25 cases/100k	\$738,140	\$470,978	\$450,611	\$514,906
≥25 cases/100k	–	\$136,377	–	\$136,377

DISCUSSION & CONCLUSION

Although CADTH has not taken an official position on acceptable economic thresholds for DRDs in Canada, it has issued numerous positive recommendations for DRDs. Our analyses confirmed that there is substantial variability in the sponsor-submitted annual per patient costs and ICERs for DRDs with positive CADTH recommendations, and that average annual treatment costs and ICERs tended to increase with disease rarity. The highest values were observed for DRDs that treat only children and “ultra-orphan” diseases (prevalence <2/100,000 population), and average ICERs in all prevalence groups exceeded the conventional willingness to pay threshold of \$50,000/QALY for non-DRD products. These findings highlight the exceptional pricing of DRDs for these special subgroups. Therefore, despite CADTH’s lack of an official position on DRDs, our analyses confirm that CADTH has made positive recommendations for DRDs based on net clinical benefit and high unmet need, despite annual costs and/or ICER values that are much higher than values for non-DRD drugs.

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