

# International time trends and differences in topical actinic keratosis therapy utilization



Heather J. Zhao, ScM,<sup>a,b</sup> Inna Ushcatz, MSc,<sup>a,b</sup> Mina Tadrous, PharmD, PhD,<sup>a,c</sup> Valeria Aoki, MD,<sup>d</sup> Aileen Y. Chang, MD,<sup>e,f</sup> Nick J. Levell, MD,<sup>g</sup> Lena Von Schuckmann, MD,<sup>h</sup> and Aaron M. Drucker, MD, ScM<sup>a,i</sup>

**Background:** Actinic Keratoses (AK) are precancerous lesions that can lead to Squamous Cell Carcinoma. International differences in the utilization of topical medications to treat AK are not well described.

**Objectives:** To describe international differences in topical AK medication utilization, including associations of countries' economic status with AK medication utilization.

**Methods:** We used IQVIA MIDAS pharmaceutical sales data for 65 countries (42 high-income, 24 middle-income) from April 2011 to December 2021. We calculated each country's quarterly utilization of medications in grams per 1000 population. We used univariable linear regression to assess the association between country economic status and AK medication utilization.

**Results:** High-income countries used 15.37 more grams per 1000 population of 5-fluorouracil (95% CI: 9.68, 21.05), 4.64 more grams per 1000 population of imiquimod (95% CI: 3.45, 5.83), and 0.32 more grams per 1000 population of ingenol mebutate (95% CI: 0.05, 0.60).

**Limitations:** Missing medication utilization data for some countries.

**Conclusion:** High-income countries use more topical AK therapies than middle-income countries. (JAAD Int 2024;16:18-25.)

**Key words:** actinic keratosis; global dermatology; international medication utilization; medication utilization; SCC; squamous cell carcinoma.

## INTRODUCTION

Actinic Keratosis (AK) is a precancerous skin condition characterized by rough scaly lesions on sun-exposed areas. If AKs are left untreated, some proportion, with estimates ranging between 0.025%

to 16%, may transform into cutaneous squamous cell carcinoma (SCC), which causes nearly 20% of skin cancer-related mortality.<sup>1-3</sup> People with more AK lesions are at higher risk of SCC.<sup>4,5</sup> Therapeutic options to treat AKs and thereby prevent SCC include

From the Department of Medicine, Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada<sup>a</sup>; Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada<sup>b</sup>; Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada<sup>c</sup>; Department of Dermatology, University of São Paulo School of Medicine, São Paulo, São Paulo Estado, Brazil<sup>d</sup>; Department of Dermatology, University of California, San Francisco, San Francisco, California<sup>e</sup>; Department of Dermatology, Zuckerberg San Francisco General Hospital and Trauma Center, San Francisco, California<sup>f</sup>; Norfolk and Norwich University Hospital, Norwich, UK<sup>g</sup>; University of Queensland, Frazer Institute, Brisbane, Queensland, Australia<sup>h</sup>; and Division of Dermatology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada.<sup>i</sup>

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Correspondence to: Aaron M. Drucker, MD, ScM, Department of Medicine, Women's College Research Institute, Women's College Hospital, 76 Grenville St, Toronto, ON M5S 1B2, Canada. E-mail: [aaron.drucker@wchospital.ca](mailto:aaron.drucker@wchospital.ca), Twitter: [@aaron\\_drucker](https://twitter.com/aaron_drucker).

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physical modalities (such as cryotherapy), photodynamic therapy, and topical medications.<sup>6,7</sup> Currently, there have been 5 topical AK treatments available internationally.<sup>6</sup> 5-fluorouracil, imiquimod, diclofenac, ingenol mebutate (which was removed from the market in across countries in 2020) and tirbanibulin.

Despite the established efficacy of topical therapy as a strategy for treating AK and preventing skin cancer, the international accessibility of these medications is not well understood. Countries' economic status, health care policies, medication availabilities, geographic locations, ethnic variations, and AK and SCC prevalence could each influence the prescription and utilization of topical AK medications.

To address these knowledge gaps, we assessed purchasing trends of topical medications used to treat AK across multiple countries, and estimated associations between countries' economic status and topical AK medication usage.

## MATERIALS AND METHODS

### Data source

We analysed IQVIA MIDAS pharmaceutical sales data for 80 countries for the period between April 2011 to December 2021. IQVIA MIDAS is a dataset which tracks sales volumes and values across 94 countries globally. It is a globally harmonised dataset, sourced from IQVIA National Sales Audits, which facilitates cross-country comparison.<sup>8</sup> We obtained quarterly sales data for each of 5-fluorouracil, imiquimod, diclofenac, and ingenol mebutate. For diclofenac, we excluded formulations other than diclofenac sodium 3% gel. We did not include tirbanibulin because it was only approved in 2021. The volume sales data we selected for analysis was in grams of medication sold. IQVIA MIDAS data include hospital and retail channels but does not include information about individual facilities. We excluded low-income countries because there were no relevant sales data available. We also excluded countries that were missing more than 50% of their total sales data, leaving 65 countries in our analysis. Of the 65 countries in our study, IQVIA MIDAS captured an average of 90% of national sales. Data capture was

92% in high-income countries and 87% in middle-income countries.

We obtained country population data from the United Nations Department of Economic and Social Affairs from 2011 to 2021.<sup>9</sup> We grouped country income status into high- and middle-income countries based on the mode income status from 2011 to

2021 according to the United Nations' World Economic Situation.<sup>9</sup> We grouped upper-middle and low-middle-income countries together as middle-income countries. There was no AK medication sales data for any low-income countries.

We obtained countries' SCC prevalence from 2011 to 2019 from the Institute for Health metrics and Evaluation Global Burden of Disease (GBD) database.<sup>10</sup> We classified country's geographic location by

hemisphere according to the World Atlas.<sup>11</sup>

### CAPSULE SUMMARY

- Actinic keratosis, a precancerous condition for squamous cell carcinoma, is treated with topical medications. However, its international medication utilization trends are not well understood.
- Higher-income countries use more topical actinic keratosis medications, but utilization rates don't align with squamous cell carcinoma prevalence, indicating incongruence between treatment need and accessibility.

### Analysis

We reported population-adjusted medication utilization rates by dividing the grams of topical AK medications sold by the country's population and presented them as grams used per 1000 population. We only included a country in analyses for a given medication if there was at least some (>0 g) utilization of that medication in that country.

To visualize AK medication utilization in 2019, we categorized each country's medication gram usage per 1000 country population into quartiles. We then plotted each country's quartile on a map using the Stata package "*spmap*." We created country density plots for 5-fluorouracil, imiquimod, diclofenac, and ingenol mebutate. We did not analyze total topical AK medication use (sum of all the medications) per country because the use of 1 gram varies between different topical AK medications.

To visualize AK medication utilization over time, we plotted quarterly medication usage by country economic status and hemisphere. We plotted utilization over time for 5-fluorouracil, imiquimod and diclofenac, and ingenol mebutate from April 2011 to December 2021.

In our primary analysis, we used univariable linear regression to estimate the association between

**Abbreviations used:**

AK:	Actinic Keratoses
GBD:	Global Burden of Disease
SCC:	squamous cell carcinoma

country economic status with AK medication utilization in 2019. In a secondary analysis, we used univariable and multivariable linear regression to estimate the association between each of country economic status and SCC prevalence with AK medication utilization in 2019. We chose 2019, rather than the more recent 2021, because 2019 is the most recent year available in the GBD database for SCC prevalence and to avoid the effects of the COVID-19 pandemic. The exposure variable, country SCC prevalence, was assessed alone in univariable analyses, and the multivariable analysis included both variables. We repeated this analysis with medication utilization from 2021 (rather than 2019) as the outcome with SCC prevalence data from 2019. We conducted another secondary analysis for factors associated with AK medication usage by hemisphere in 2019.

All statistical analyses were conducted using Stata v.16.

**RESULTS**

Among the 65 countries with AK therapy sales from April 2011 to December 2021, 42 were high-income and 23 middle-income. A total of 53 countries used 5-fluorouracil (37 high-income and 16 middle-income), 65 countries used imiquimod (42 high-income and 23 middle-income), 14 countries used diclofenac (14 high-income and 0 middle-income), and 30 countries used ingenol mebutate (26 high-income and 4 middle-income). For all medications, utilization was highest in the fourth quarter of each year.

**AK treatment utilization trends by geography**

In 2019, there were 37 northern hemisphere and 7 southern hemisphere countries with utilization of 5-fluorouracil, 50 northern and 8 southern countries with utilization of imiquimod, and 21 northern and 2 southern countries with utilization of ingenol mebutate. There was only 1 southern hemisphere country and 13 northern countries with utilization of diclofenac.

In 2019, countries in the third and fourth (highest) quartiles for 5-fluorouracil and imiquimod utilization were primarily from North America, Europe, and Australia (Fig 1, A and B). Only Western European countries and Australia used diclofenac (Fig 1, C).

Countries in the third and fourth quartile for ingenol mebutate utilization were from Western Europe and Australia (Fig 1, D).

There was higher utilization of 5-fluorouracil and imiquimod among countries in the southern hemisphere compared to the northern hemisphere (Supplementary Fig 1A and B, available via Mendeley at <https://data.mendeley.com/datasets/ppftwcs7zr/1>). For ingenol mebutate, utilization was higher among countries in the northern hemisphere from 2013 quarter 1 until 2020 quarter 2, after which utilization was equal in countries from both hemisphere (Supplementary Fig 1C, available via Mendeley at <https://data.mendeley.com/datasets/ppftwcs7zr/1>).

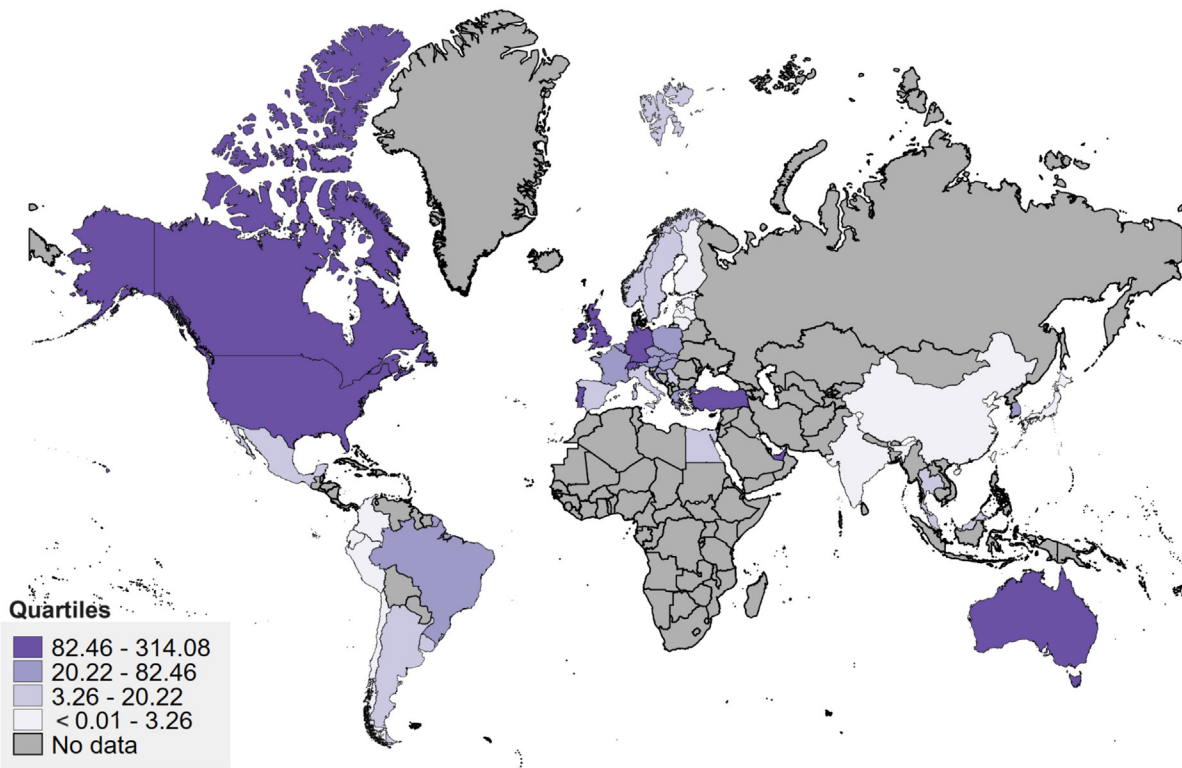
**AK treatment utilization trends by country economic status**

From April 2011 to December 2021, there was a gradual increase in 5-fluorouracil utilization in high-income countries but not in middle-income countries (Supplementary Fig 2A, available via Mendeley at <https://data.mendeley.com/datasets/ppftwcs7zr/1>). Imiquimod utilization was relatively stable over that time (Supplementary Fig 2B, available via Mendeley at <https://data.mendeley.com/datasets/ppftwcs7zr/1>). For diclofenac, there was a gradual increase in utilization until 2018 quarter 4, followed by a decrease until 2020 quarter 2, with a resumed increase (Supplementary Fig 2C, available via Mendeley at <https://data.mendeley.com/datasets/ppftwcs7zr/1>). Ingenol mebutate utilization started in 2012 quarter 2 among high-income countries, and in 2013 quarter 1 among middle-income countries. In high-income countries, ingenol mebutate utilization continued to increase until market removal in 2020 quarter 2 (Supplementary Fig 2D, available via Mendeley at <https://data.mendeley.com/datasets/ppftwcs7zr/1>).

**Association between economic status, SCC prevalence, and hemisphere with AK treatment utilization**

High-income countries used 15.37 more grams per 1000 population of 5-fluorouracil (95% CI: 9.68, 21.05), 4.64 more grams per 1000 population of imiquimod (95% CI: 3.45, 5.83), and 0.32 more grams per 1000 population of ingenol mebutate (95% CI: 0.05, 0.60) in 2019 compared to middle-income countries (Table 1). Only high-income countries used diclofenac.

In our secondary analysis, topical AK medication utilization was less clearly associated with SCC prevalence (Supplementary Table 1, available via Mendeley at <https://data.mendeley.com/datasets/ppftwcs7zr/1>).



**A** Map template obtained from World Bank

**Fig 1. A,** International 5-Fluorouracil Utilization in 2019. Utilization is presented as grams per 1000 Population, with colour categorization by quartiles ( $N = 44$  countries). **B,** International Imiquimod Utilization in 2019. Utilization is presented as grams per 1000 Population, with colour categorization by quartiles ( $N = 58$  countries). **C,** International Diclofenac Utilization in 2019. Utilization is presented as grams per 1000 Population, with colour categorization by quartiles ( $N = 14$  countries). **D,** International Ingenol Mebutate Utilization in Different Countries in 2019. Utilization is presented as grams per 1000 Population, with colour categorization by quartiles ( $N = 23$  countries). Author analysis based on IQVIA MIDAS quarterly volume sales data for January- December 2019, reflecting estimates of real-world activity. Copyright IQVIA. All rights reserved.

ppftwcs7zr/1). For every percent increase in SCC prevalence, there was an increased use of 5-fluorouracil (7.20 grams per 1000 population, 95% CI: 0.45, 13.94), but statistically non-significant increase of imiquimod (0.74 grams per 1000 population, 95% CI:  $-1.13, 2.61$ ), decrease of diclofenac ( $-42.27$  grams per 1000 population, 95% CI:  $-87.17, 2.59$ ), and decrease of ingenol mebutate ( $-0.10$  grams per 1000 population, 95% CI:  $-0.21, 0.01$ ). The association between SCC prevalence and 5-fluorouracil use was no longer statistically significant ( $P > .05$ ) when adjusting for country economic status in 2019 but was significant when using utilization data from 2021 (7.51 grams per 1000 population, 95% CI: 2.18, 12.84) (Supplementary Table II, available via Mendeley at <https://data.mendeley.com/datasets/ppftwcs7zr/1>). When repeating the analysis using utilization data from 2021, results

were similar to our primary and secondary outcomes; high-income countries used more topical AK medication compared to middle-income countries, and topical AK medication utilization was less clearly associated with SCC prevalence (Supplementary Table II, available via Mendeley at <https://data.mendeley.com/datasets/ppftwcs7zr/1>).

When stratifying by hemisphere, for every 1% increase in SCC prevalence, there was increased medication usage per 1000 population in countries from the Southern hemisphere (5-fluorouracil: 91.60 grams, 95% CI 78.66, 104.54; imiquimod: 38.75 grams, 95% CI 36.11, 41.37; ingenol mebutate: 0.72 grams, 95% CI 0.61, 0.83) but not for countries in the northern hemisphere (Supplementary Table III, available via Mendeley at <https://data.mendeley.com/datasets/ppftwcs7zr/1>). In both hemispheres, high-income countries use more medication per

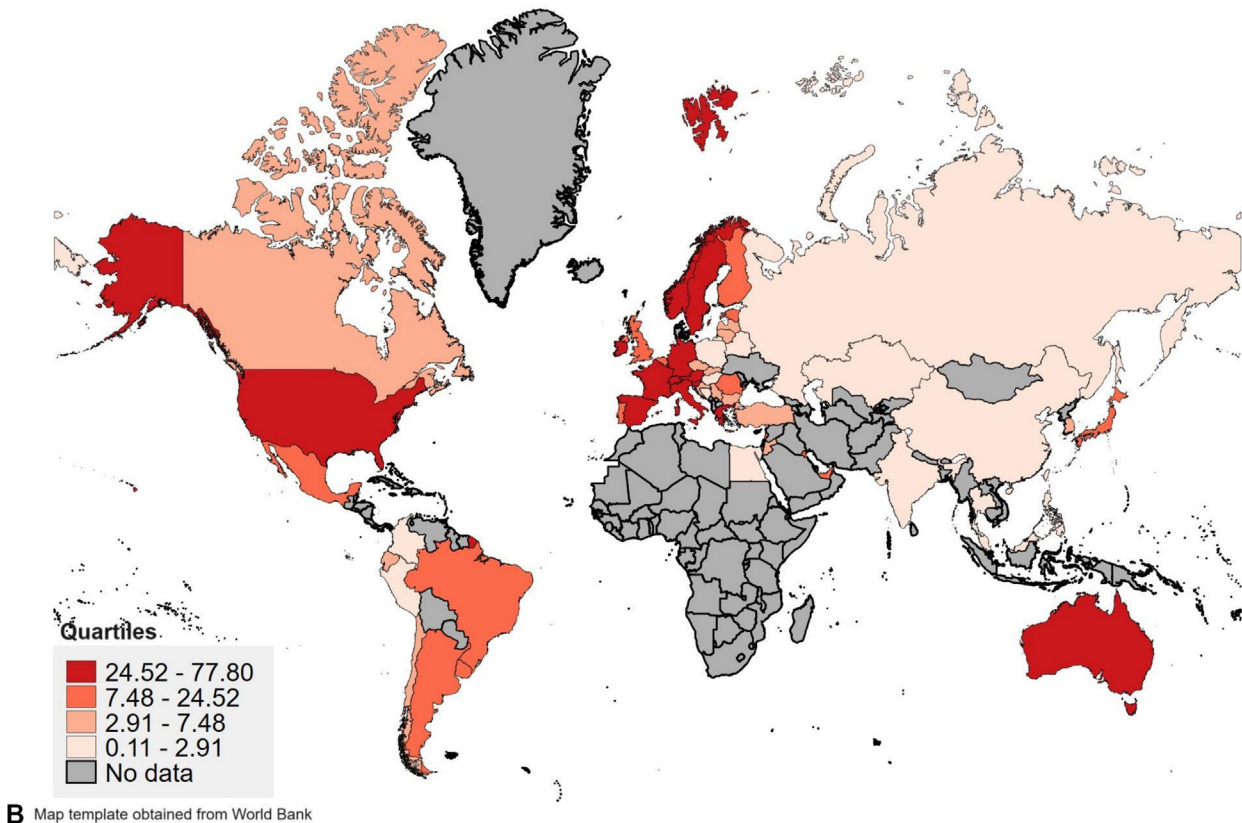


Fig 1. Continued.

1000 population than middle-income countries. The association was no longer significant for countries in the southern hemisphere when adjusting for SCC prevalence.

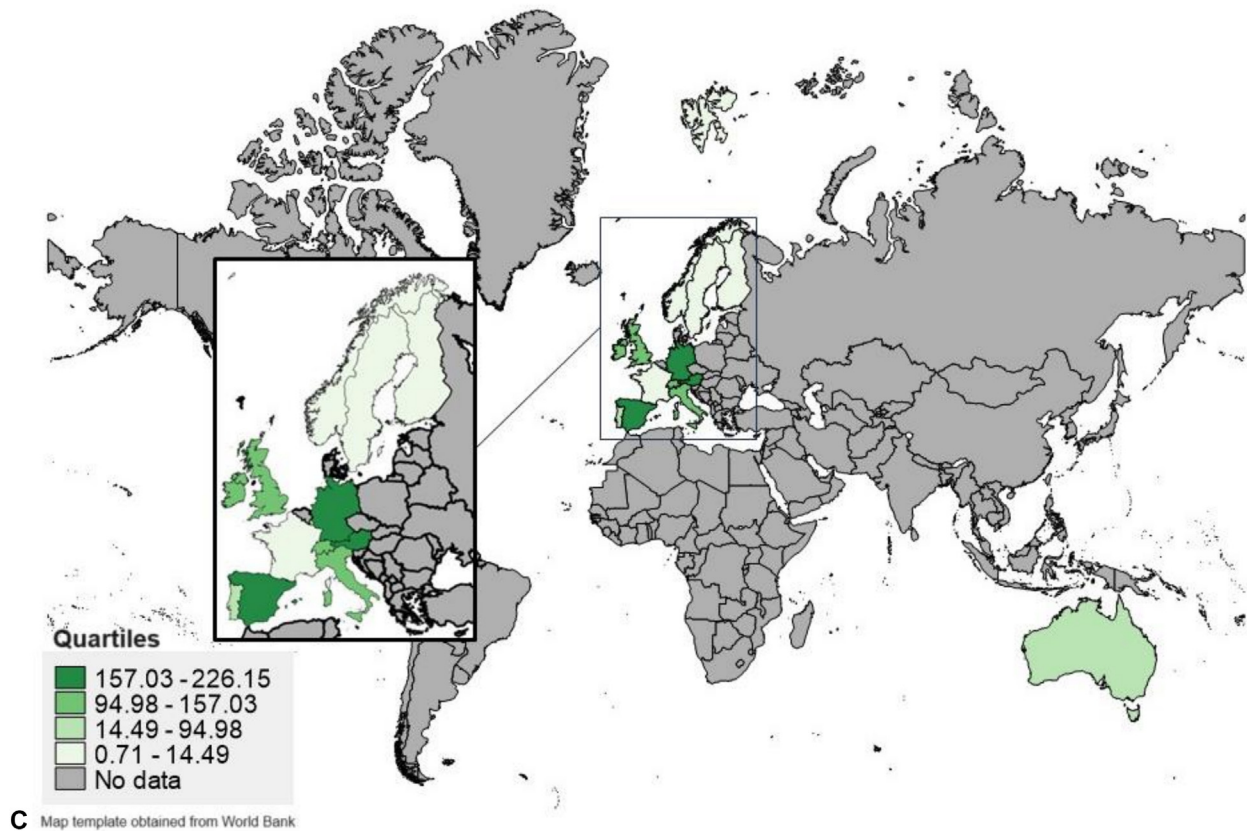
## DISCUSSION

In this analysis of international AK medication utilization, high country economic status was associated with increased topical AK treatment utilization independent of SCC prevalence. There was higher use of topical AK medication use in the southern hemisphere.

Topical AK medication utilization increased overall from 2011 to 2021, which is paralleled by the increasing global prevalence of squamous cell carcinoma. Global SCC prevalence is estimated to have risen by 310% from 1990 to 2017.<sup>3</sup> During the COVID-19 pandemic, there was a decrease in global diagnosis of keratinocyte carcinomas including SCC, and 69% of dermatologists reported a decreased quality of care.<sup>12,13</sup> This trend is also reflected in our study which found a decline in utilization of all 4 topical AK medications in the second quarter of 2020.

Our finding that the countries in the southern hemisphere had more topical AK use per population may be partially explained by AK prevalence in Australia, which makes up the majority of the southern hemisphere's topical AK utilization in our study. The prevalence of AKs has been reported to be 11%-25% in the northern hemisphere<sup>14</sup> and 40% in Australia, which Australia has the one of the highest rates of SCC globally due to high UV exposure and a high proportion of lighter-skinned individuals.<sup>15,16</sup>

Global utilization of imiquimod was stable over time, whereas 5-fluorouracil utilization increased. Initial assessment for facial AK in clinical trials showed imiquimod to be similarly efficacious to 5-fluorouracil with a 100% AK clearance in 45% to 84% of patients depending on application frequency,<sup>17,18</sup> and no difference in short- or long-term risk of SCC progression.<sup>19</sup> However, recent systematic reviews and a large clinical trial showed that 5-fluorouracil is the most efficacious field-directed therapy for AK,<sup>20-22</sup> which may partly explain our findings of the steady increase of 5-fluorouracil utilization. In addition to efficacy,



**Fig 1.** Continued.

lower cost may further contribute to 5-fluorouracil's higher utilization.<sup>23</sup>

Diclofenac sodium 3% gel and ingenol mebutate are less commonly used topical AK medications approved by the Food and Drug Administration in October 2000 and January 2012, respectively.<sup>24,25</sup> In a randomized trial, 5-fluorouracil exhibited superior AK clearance to diclofenac, while diclofenac garnered higher satisfaction ratings among users than 5-fluorouracil (93.3% vs 38.4%,  $P = .008$ ).<sup>26</sup> Higher costs and greater tolerability, balanced against lower efficacy, could explain why diclofenac was exclusively used in high-income countries.<sup>26</sup>

Compared to 4 or more weeks of topical AK treatment with other medications, ingenol mebutate gained favorability among patients and clinicians for its short treatment duration of 2-3 days.<sup>27</sup> A Markov-stimulated hypothetical AK cohort estimated that ingenol mebutate had lower total cost of treatment than diclofenac.<sup>28</sup> These features may explain ingenol's rapid adoption after its approval. Subsequently, we found that ingenol mebutate utilization had the greatest decline from the first quarter of 2020 during which the European Union and other regulators withdrew the medication from market due to its association with increase incidence of skin cancer.<sup>29,30</sup>

Our study has notable strengths: we used IQVIA MIDAS international pharmaceutical sales data that captured hospital and retail sales without restrictions on insurance coverage, age category, or income, providing a generalizable overview of utilization patterns within the included countries. Although our multivariable adjustment did not include countries' average age, adjusting for SCC prevalence, which would be higher in countries' with older populations, does so indirectly and in a way that more precisely accounts for potential confounding by the association of increasing age with increasing AK prevalence.<sup>31</sup> SCC prevalence also serves as an indirect proxy for skin pigmentation, because more lightly pigmented skin is associated with increased SCC risk.<sup>31</sup>

### Limitations

Our study has important limitations. First, IQVIA MIDAS data do not have data on every country worldwide, as collecting data from some of the lower income countries is more challenging, so our findings may not be generalizable globally. Secondly, the data only includes sales data which excludes information about individual facilities and includes only the channels of distribution audited by IQVIA which,

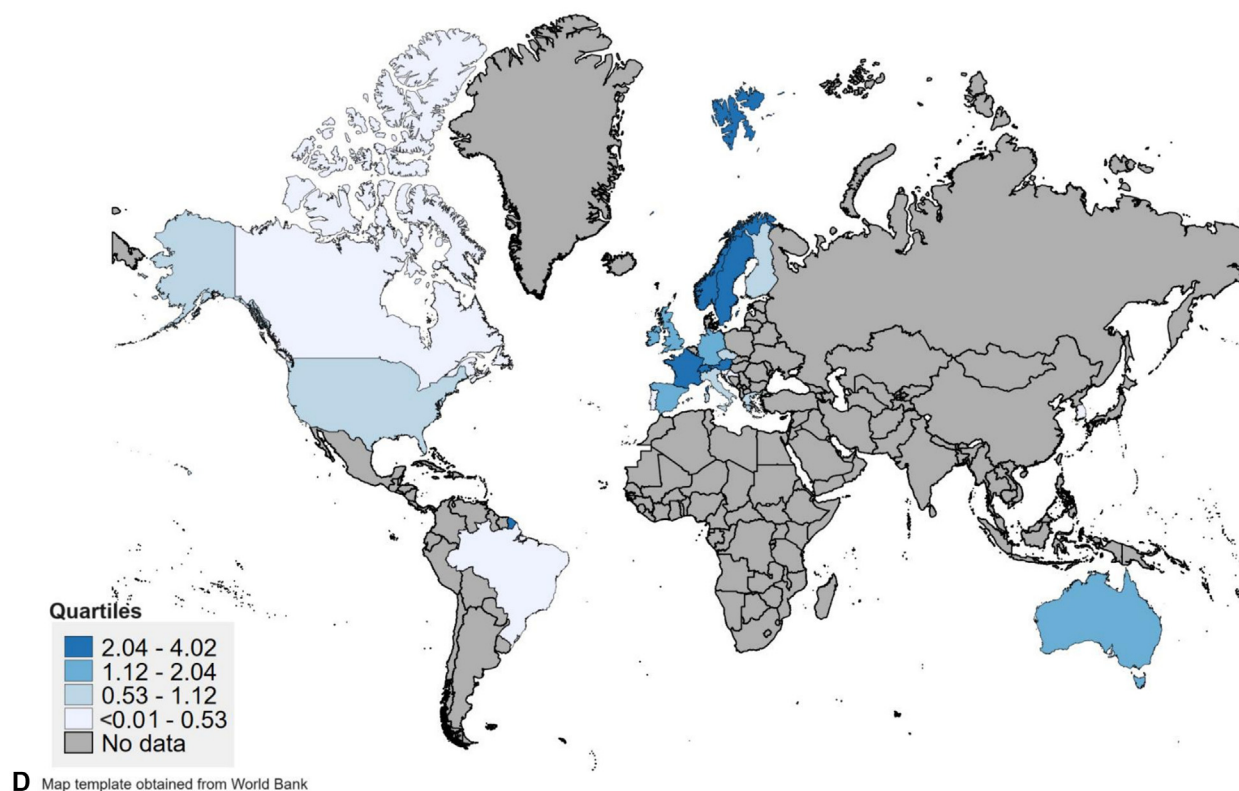


Fig 1. Continued.

**Table I.** Association of country economic status with topical actinic keratosis medication utilization in 2019. Results are given as the difference in grams used per 1000 population

	Number of countries with utilization	Difference in medication utilization between high-income and middle-income (ref) countries (95% CI)
5-Fluorouracil	High-income: 31 Middle-income: 13	15.37 (9.68, 21.05)
Imiquimod	High-income: 37 Middle-income: 21	4.64 (3.45, 5.83)
Diclofenac	High-income: 14 Middle-income: 0	n/a
Ingenol mebutate	High-income: 22 Middle-income: 1	0.32 (0.05, 0.60)

Author analysis based on IQVIA MIDAS quarterly volume sales data for January- December 2019, reflecting estimates of real-world activity. Copyright IQVIA. All rights reserved.

depending on the country, may or may not include direct sales distribution from manufacturer to pharmacy. We do not have data on the approval status and availability of each medication in every country included in the analysis, but we only include countries in a given analysis if there are at least some sales of the relevant medication. Additionally, we do not have data on the utilization of other AK treatment modalities such as liquid nitrogen cryotherapy. Furthermore, the GBD database may not accurately estimate SCC prevalence per country.

Lastly, topical 5-fluorouracil and imiquimod may be used for conditions other than AK, such as warts, Bowen's disease, and basal cell carcinoma.<sup>32,33</sup> For diclofenac, we limited the included formulations to diclofenac sodium 3% gel that is exclusive to AK treatments.

## CONCLUSION

Countries with higher income status use more AK topical therapies independent of SCC prevalence.

Data from this study was supported by funds from CIHR grants.

### Conflicts of interest

MT received consulting fees from CADTH and Health Canada. NJL is a trustee of the British Association of Dermatologists. AMD has received compensation from the British Journal of Dermatology (reviewer and Section Editor), American Academy of Dermatology (guidelines writer), National Eczema Association (grant reviewer), Canadian Dermatology Today (manuscript writer) and Canadian Agency for Drugs and Technologies in Health (consultant). AMD has received research grants to his institution from the National Eczema Association, Eczema Society of Canada, Canadian Dermatology Foundation, Canadian Institutes for Health Research, US National Institutes of Health and Physicians Services Incorporated Foundation.

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