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Worldwide rates of diagnosis and effective treatment for cystic fibrosis

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ABSTRACT

Background: Time has seen management for Cystic Fibrosis (CF) advance drastically, most recently in the development of the disease-modifying triple combination therapy ivacaftor/tezacaftor/elexacaftor. There is currently limited evidence regarding both the global epidemiology of CF and access to this transformative therapy - and therefore where needs are not being met. Therefore, this study aims to define gaps in access to CF treatment.

Methods: Patient data were extracted from established CF registries. Where these were not available, literature searches were conducted alongside an international survey of 51 CF experts to determine the diagnosed patient population. National CF prevalence estimates were combined with registry data on estimated population coverage, to extrapolate the total estimated number of undiagnosed patients. Estimates of ivacaftor/tezacaftor/elexacaftor treatment coverage were extracted from publicly available sales summaries and pricing data.

Results: 162,428 [144,606–186,620] people are estimated to be living with CF across 94 countries. Of these, an estimated 105,352 (65%) are diagnosed, with 19,516 (12%) receiving triple combination therapy. We estimated 57,076 patients with undiagnosed CF. Owing to a paucity of high-quality data, estimates of undiagnosed CF in low- and middle-income countries are highly uncertain. Patient registries were available in 45 countries, and used to identify 90% of the estimated diagnosed population.

Conclusions: A significant CF patient burden exists in countries where disease-modifying drugs are unavailable, and final figures are likely underestimates. This analysis shows the potential to improve rates of diagnosis and treatment for CF, so a higher percentage of patients receive the most effective triple combination treatment.

1. Introduction

Cystic fibrosis (CF) has traditionally been thought of as a disease affecting exclusively Caucasians of European descent, and therefore only prevalent in Europe, North America, and Australasia [2,3]. However, recent evidence shows the condition is also present – albeit generally at lower rates – in other regions such as the Middle East, Asia, and Latin America [4,5]. Although absolute incidence rates may be lower, the large population contained within these regions means the disease burden could still be substantial.

This existing preconception means that it is almost exclusively high-income countries (HICs) in the global north which have established systematic CF patient registries, which are vital for epidemiological research [6]. Consequently, little is known of the epidemiology of CF in low- and middle-income countries (LMICs) [4,7], and while estimates in the literature range from 70,000–90,000 it is unknown how many people have CF worldwide [8,9].

The sequencing of the cystic fibrosis transmembrane conductance regulator (CFTR) gene has led to the development of small molecule therapies targeting the root cause of CF, known as CFTR modulators [8,10]. Four such treatments are currently licensed and sold by Vertex Pharmaceuticals (Table 1). The most recent of these – the triple combination ivacaftor/tezacaftor/elexacaftor – is suitable for a larger proportion of mutation profiles compared to previous generation therapies. Furthermore, in randomised trials versus both placebo and previous generation dual therapy [11], ivacaftor/tezacaftor/elexacaftor has shown significantly improved outcomes as measured via lung function (FEV_1) and quality of life (CFQ-R score). Therefore, this paper will focus on ivacaftor/tezacaftor/elexacaftor.

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Table 1
Comparison of current dual and triple CFTR modulator therapies in terms of formulation, efficacy, and eligibility [10]. Only Orkambi, Symdeko, and Trikafta have been included due to their comparable eligible populations. One year list prices represent costs in the US market.

Brand name	Active pharmaceutical ingredients	FEV_1 change vs placebo	CFQ-R score change vs placebo	CF mutation eligibility	Percentage of CF population eligible	Year licensed	Estimated patent expiry	One year list price
Orkambi	Ivacaftor/ lumacaftor	2.8% improvement	2.2 score increase	Homozygous f508del	50%	2015	2030	$272,623
Symdeko	Ivacaftor/ tezacaftor	4% improvement	5.1 score increase	Homozygous f508del or heterozygous f508del-residual function mutation	55%	2018	2027	$292,200
Trikafta	Ivacaftor/ tezacaftor/ elexacaftor	13.8% improvement	22.5 score increase	At least one f508del mutation irrespective of the second mutation	90%	2019	2037	$311,741

FEV_1 = Forced Expiratory Volume in one second.
CFQ-R = Cystic Fibrosis Questionnaire Revised, a disease-specific health-related quality of life measure.

CFTR modulators represent an unparalleled opportunity to increase quality and length of life for almost all CF patients [7,8]. Yet their list prices have been set between $270,000–310,000 per annum for a condition requiring a lifetime of treatment. This means even after regulatory approval, the medicines are so expensive they are essentially unavailable unless reimbursed by government or health system authorities. In Poland, where no modulators are available, the median life expectancy for CF remains at 24.5 years compared to 46 in the USA [12,13]. As such, the extreme cost of CFTR modulators could serve to only widen existing disparities [5,14]. Despite this, there exists relatively little literature concerning global patient access to these emergent therapies.

Perhaps the most notable success in access to medicines is the case of triple combination antiretroviral therapy used for the treatment of human immunodeficiency virus (HIV). Similarly prohibitive drug prices were reduced by over 99%, allowing millions access in resource-poor settings [15]. Progress in this therapeutic area is often displayed via the "treatment cascade" framework; depicting the proportion of patients diagnosed and treated worldwide. This framework has since been used for other conditions such as TB and opioid addiction [16,17], and so could be applied to CF to highlight disparities in diagnosis and treatment access.

Therefore, using the precedent set in the case of HIV, this study aims to define gaps in access to CF treatment. This will be achieved via construction of a treatment cascade to present a novel characterisation of the epidemiology of CF - involving generation of point estimates of the total global CF population, proportion diagnosed, and proportion treated with triple therapy.

2. Methods

2.1. Sources of data

A total of 158 countries were included in this analysis. Countries with a total population of less than one million and no patient registry were excluded, as there was unlikely to be a significant patient population or available data. Owing to the paucity of epidemiological data in many settings, a variety of methods were employed.

The most recent publicly available patient data were extracted from all established CF registries. Where such registries did not exist, PubMed literature searches were conducted to identify previously aggregated regional data, surveys, or case reports of patient numbers in individual countries, as well as epidemiological studies estimating national prevalence of CF. The search term "*cystic fibrosis*" was combined separately with 113 country names and four geographical regions (full search strategy can be found in Appendix 1). Search results dating back to 1960 were included to assess the quantity of the evidence available for each country, however only studies from the year 1991 onward were included in the final analysis. In addition, an international survey of CF experts and patient organisations was conducted through email communications and virtual interviews (questions/topics covered can be found in Appendix 2). Snowball sampling was used to generate contacts from an initial sample of seven derived from collaboration with CF families, for a final total of 51 contacts.

2.2. Diagnosed patient population

Where multiple values of diagnosed patient population were obtained for a single country, factors such as the number of patients (due to the likelihood of systemic underreporting), year of data collection, number of facilities included, and quantity of available literature determined which was selected. All patients included within country-level data were registered within their respective countries' health systems. Diagnosis was performed using sweat testing at a minimum; in some cases, genetic analysis was used instead.

Following estimation of diagnosed population CF prevalence was calculated to provide a method of comparison between countries/regions. All prevalence values provided per continent are given as mean ± standard deviation (SD).

2.3. Undiagnosed patient population

To estimate the number of undiagnosed CF patients, where available, registry data detailing estimated patient coverage were used to extrapolate the total number of patients within each country. If this was given as a range rather than a specific percentage, the midpoint of the lower bound and 100% coverage was used. Where possible, cross-sectional analyses estimating national CF prevalence were extrapolated to generate expected CF patient numbers. Additionally, estimations were made as part of the CF survey.

Following estimation of diagnosed and undiagnosed patient population, the two values were combined to generate an estimate of the total global CF disease burden.

2.4. Patient treatment access

Information on the number of patients treated with ivacaftor/tezacaftor/elexacaftor was not publicly available. Therefore, to estimate this value, sales revenues were extracted from Vertex's 2020 End of Year earnings report. Only fourth quarter revenues were included to ensure greater accuracy, since regulatory approval in several markets was achieved mid-year. Proportions of Vertex's revenue by geographical region (US, EU, and other ex-US/EU) were calculated for the last three years using data published within the company's annual Securities and Exchange Commission filings. An average was taken and applied to 2020 revenues to estimate the proportion of revenue from each region. Ex-US/EU market share was reallocated to the US, as this currently represents the main

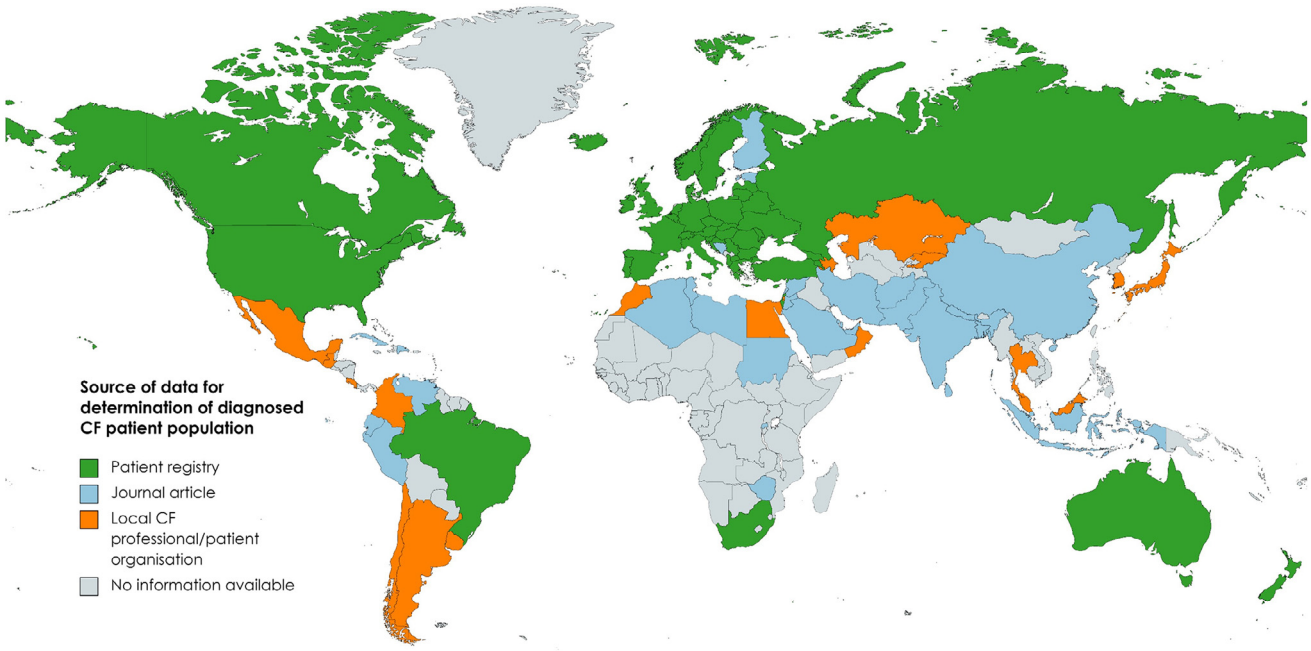

Fig. 1. Map displaying methods used to obtain estimates of diagnosed CF patient burden in each country. Although a registry is kept in Argentina this was being restructured and so data was retrieved from a local CF professional.

market and ivacaftor/tezacaftor/elexacaftor has not been approved outside of the US and EU [18].

The lowest price available in each region for a three-month treatment course was determined through public pricing databases and used to estimate the number of patients receiving triple therapy [19,20]. A further 25% discount was assumed resulting from negotiations with payors [21].

2.5. Sensitivity analysis

The largest source of uncertainty within our collected data resided in our estimate of the undiagnosed CF population. As such, in accordance with other studies utilising treatment cascades we produced lower and upper limits of this estimate to provide additional context for interpretation [22]. This was achieved by incorporating maximum and minimum estimates of:

- Identified registry coverage data (where this was given as a range).
- Expected CF populations in countries with multiple prevalence estimates.
- Uncertainty intervals for estimates provided by CF experts.

3. Results

3.1. Diagnosed patient population

A total of 2875 articles were retrieved from PubMed and 28 replies received from the CF survey, for a response rate of 55%. At a country-level, 45 results were obtained from registry data, 18 from national CF experts, and 31 from literature sources. For 64 countries no information could be found (Fig. 1). A flow diagram depicting provenance of country-level data can be found in Appendix 3.

Worldwide, 105,352 people from 94 countries are estimated to have been diagnosed with CF (Fig. 2), with 90% of this population identified from patient registries. All identified results can be found in Appendix 4.

3.1.1. Europe

There were 47,650 estimated diagnosed patients in 40 countries. Mean prevalence in Europe was 0.548±0.48. A high level of reporting infrastructure exists in Europe, with registry data available for 37 countries. Registry coverage was notably lower in Eastern European countries such as Lithuania, Ukraine, and Poland, potentially accounting for the smaller patient burden observed in these jurisdictions.

3.1.2. North America

There were 37,002 estimated diagnosed patients in seven countries. Mean prevalence in North America was 0.347±0.46. Most patients were found in the USA and Canada, where robust registries are in place. It is estimated these registries cover virtually every patient diagnosed with CF in their respective countries. Limited information was available regarding Caribbean and Central American countries, likely contributing to the high variance seen in mean prevalence.

3.1.3. South America

There were 10,034 estimated diagnosed patients in eight countries. Mean prevalence in South America was 0.244±0.19. Most of these patients were in Brazil and Argentina, where registries do exist but lack the robust coverage of those in North America or Europe. In most other countries efforts had been made to quantify the CF patient population, albeit not formally through registries. In four out of eight countries absolute patient burden was greater than 500, despite limited reporting infrastructure.

3.1.4. Australasia

There were 3652 estimated diagnosed patients in two countries. Mean prevalence in Australasia was 1.161±0.16. All identified patients were found via the patient registries of Australia and New Zealand, with no data available for Papua New Guinea. Registry systems in these countries are sophisticated, estimating near complete coverage, owing to their high levels of economic development and established prevalence of CF.

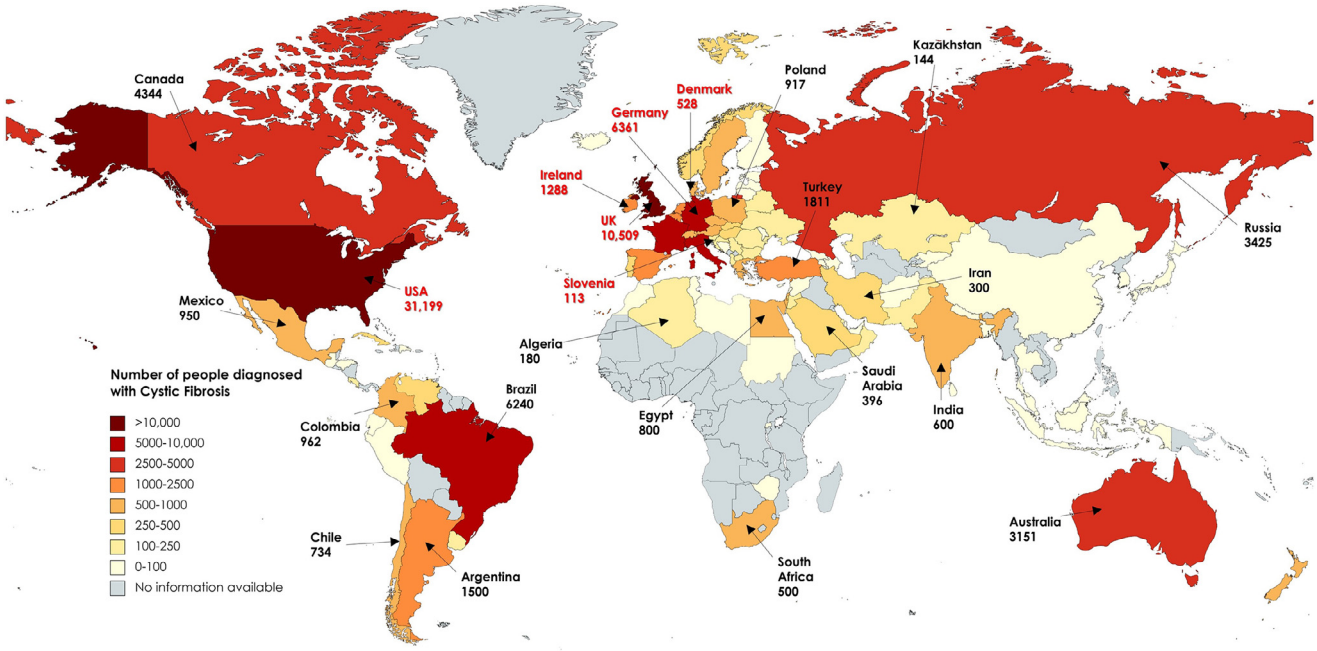

Fig. 2. Map displaying the estimated diagnosed CF patient burden around the world. Selected populations have been labelled either due to significant absolute size or lack of previous epidemiological characterisation. Countries labelled in red font had reimbursement agreements in place for ivacaftor/tezacaftor/elexacaftor at the end of 2020.

3.1.5. Asia

There were 5349 estimated diagnosed patients in 28 countries. Mean prevalence in Asia was 0.131±0.22. Registry data were available for Israel and Turkey. While in Israel registry coverage was high, in Turkey this was estimated at just 50%. In most other Middle Eastern countries efforts had been made to estimate the epidemiology of CF, with the mean prevalence for the Middle East alone 0.264±0.27.

In Central and Eastern Asia much less information was available pertaining to CF, with no registry data available. Literature sources largely consisted of limited case reports due to the lack of diagnostic infrastructure, and no information was available in many countries.

3.1.6. Africa

There were 1665 estimated diagnosed patients in nine countries. Mean prevalence in Africa was 0.035±0.03. As seen in Fig. 2, most patients were in Egypt and South Africa. However, outside of these countries, very little information exists regarding CF in this continent with no information available in 40 countries, mostly in Sub-Saharan Africa.

3.2. Undiagnosed patient estimate

Estimates of undiagnosed patient burden were possible in 49 countries, of which 38 were from registry coverage data, eight extrapolations from epidemiological studies, and three reported from the CF survey. No information was available in 109 countries. A flow diagram depicting provenance of country-level data can be seen in Appendix 5, and all identified results can be found in Appendix 6.

The undiagnosed CF population was estimated to be 57,076 people in 49 countries, with a resulting total global disease burden of 162,428 people in 94 countries. The maximum bound of the estimated total CF population was 186,620 and the minimum bound 144,606.

Most of the undiagnosed patient burden was located in India, where several estimates of CF prevalence have been made - many of these analysing populations of Indian migrants in countries with registries such as Canada and the USA. Extrapolated estimates indicated a CF patient burden of 37,406 in India (Appendix 7). Other countries where significant undiagnosed patient populations were extrapolated from prevalence estimates include Morocco, the UAE, Oman, and Japan (Fig. 3). In Turkey, Argentina, and Egypt, the existing patient population diagnosed but not formally recorded was estimated by local CF experts.

3.3. Access to triple therapy

By the end of 2020 reimbursement agreements for ivacaftor/tezacaftor/elexacaftor were only in place in the USA, UK, Ireland, Denmark, Germany, and Slovenia. The three-year mean of Vertex's geographical revenue split between the US and European markets was 76% and 19% respectively. After reallocation of the five percent attributed to ex. US/EU jurisdictions this rose to 81% and 19%. Fourth quarter revenues for triple combination therapy in 2020 amounted to $1.1 billion. The lowest price found in the European market was the UK price of $254,000, extracted from the BNF [19]. For the US market the list price of $311,053 was used. Following application of assumed discounts this model estimated 15,152 patients in the US and 4364 in Europe, with a total estimate of 19,516 patients receiving treatment with triple therapy. Exact figures used in calculations can be found in Appendix 8.

3.4. CF treatment cascade

Of the 162,428 people estimated to have CF worldwide, currently 64.9% are diagnosed and 12% are receiving triple combination therapy (Fig. 4).

4. Discussion

This study presents novel estimates of the global epidemiology of CF. Patient registries were used to identify 90% of the estimated diagnosed population, amounting to a baseline of 95,835 patients obtained from the highest available standard of information. Data used in this study were extracted from a variety of

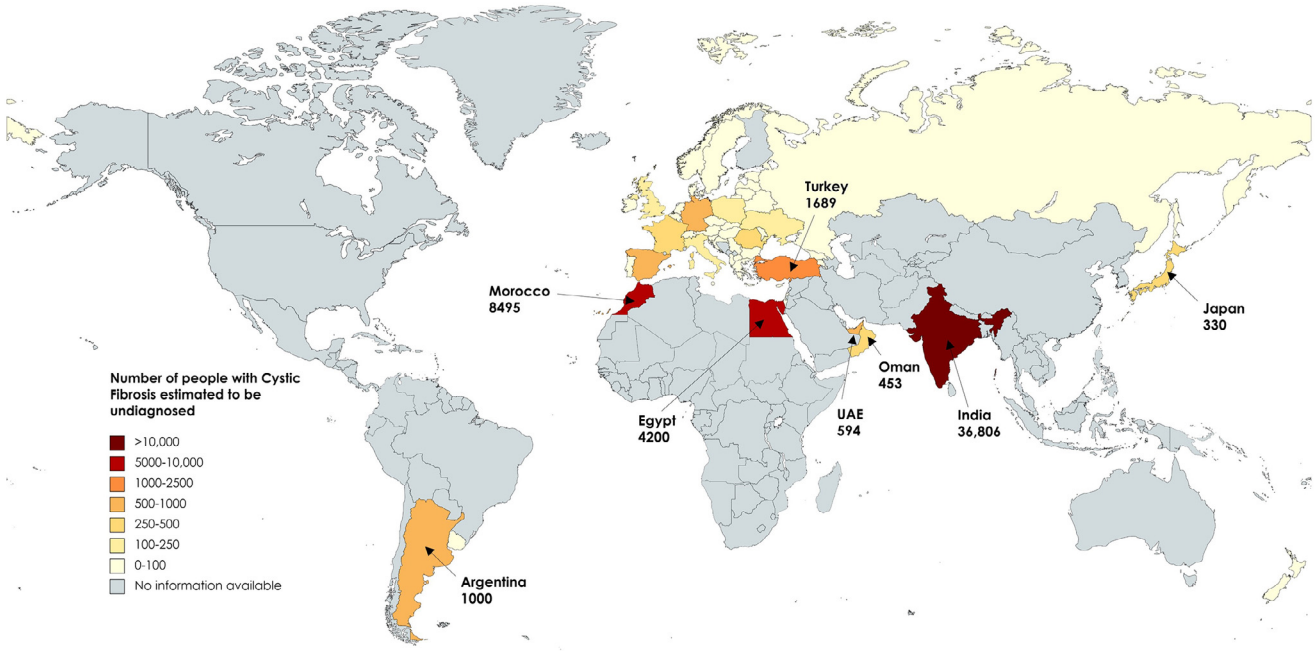

Fig. 3. Map displaying the estimated number of undiagnosed CF patients around the world. Labelled countries showed a significant undiagnosed population estimated by epidemiological studies or local CF experts.

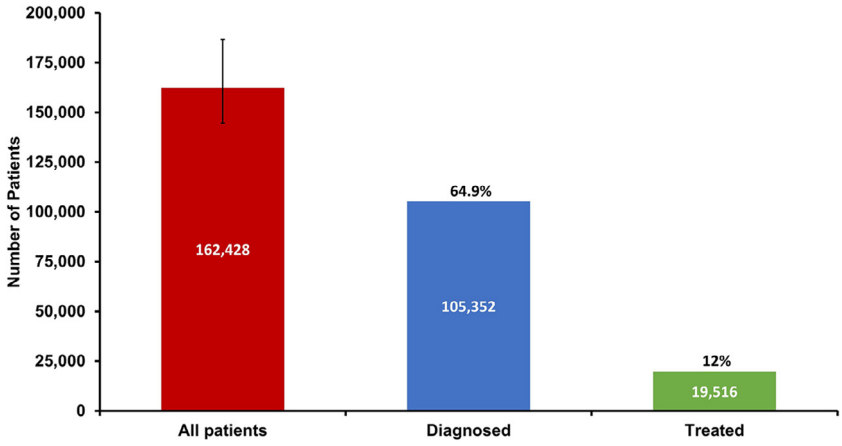

Fig. 4. Bar chart displaying treatment cascade for cystic fibrosis. Total number of patients, number of diagnosed patients and number treated with triple combination therapy are shown.

sources, including communications with CF professionals, conference proceedings, and scientific literature. This multimodal approach provided up to date information in areas lacking robust reporting infrastructure [2,4,23]. Individually, similar methods have been used in other studies aiming to characterise CF patient burden at a regional/national level [3,23,24]. The limited rollout of ivacaftor/tezacaftor/elexacaftor outside of the USA increases the accuracy of the estimated number of patients receiving treatment, due to the lower number of unique reimbursement deals/prices negotiated. However, due to the lack of information on exact per patient prices paid by health systems there remains a degree of uncertainty.

The mixed methodology used to generate data was necessitated by the well-documented paucity of epidemiological data in many LMICs [7,25,26]. However, it also meant provenance of data varied between countries. Consequently, even within continents, country-level results present data of varying quality and completeness alongside each other, and for many countries, no data was available at all. This applied to our estimates of both total and diagnosed CF population. In particular, many of the prevalence estimates used to extrapolate undiagnosed CF populations in countries without registries utilised small sample sizes, likely owing to the limited scale of CF research in these jurisdictions.

Together these factors limit the validity of our data and are demonstrated in the large SD associated with mean prevalence rates per continent, as well as in the size of the range provided for the total CF population. They reflects gaps in the evidence for the epidemiology of CF identified by our study and show that at this point in time epidemiological estimates to the standard seen in the global north are infeasible on a worldwide scale. However, the primary aim of our analysis was not to accomplish this, but rather to identify gaps in diagnosis and treatment. These remain evident in the results presented - even the minimum bound of our estimate of the total CF population represents a significant increase on contemporary figures within the literature [8,9].

Although we were able to provide a range for the total CF population there was insufficient data to provide similar sensitivity analyses for the other estimates forming the cascade. However, due

to the methodology used in estimating the diagnosed CF population, alongside the large number of countries for which incomplete or no epidemiological data were found, our estimate of the global diagnosed population remains conservative. Other limitations to the precision of our estimates include the novelty of triple combination treatment meaning negotiations and drug rollout is ongoing in some settings, alongside inclusion of literature results from the past 30 years - in many LMICs the average life expectancy of a CF patient is lower than this [7,13,26].

While genetic analyses utilising populations of non-Caucasian ethnicity have found f508del to still be the most common disease-causing mutation, it is not as dominant as observed in Caucasian populations [27]. Consequently, in some LMICs, a lower proportion of patients may be eligible for triple therapy. However, approval has recently been granted for ivacaftor/tezacaftor/elexacaftor to be used to treat 117 rare non-f508del mutations [28], and further epidemiological studies are required to more accurately define mutation profiles worldwide before conclusions can be drawn.

A key theme which emerged from the CF survey and literature results was the underdiagnosis of CF in LMICs [7,25,26]. In these regions, the substantial public health challenges posed by communicable disease means governments may be less willing to allocate resources to comparatively rare diseases such as CF. Therefore, in some settings there may only be a few sweat testing machines supplying the entire country, or none at all [26,29]. This was displayed in the significantly larger expected compared with diagnosed populations in LMICs where genetic screening had been used to estimate CF prevalence.

As such, the paucity of epidemiological data and underdiagnosis in LMICs remain key barriers to effective and equitable treatment. However, in recent years there has been increasing recognition of the need for additional CF research and awareness in these regions [4,7,23,26]. Given the lack of registries, opportunities to estimate the epidemiology in these areas with greater accuracy could include mathematical modelling, or further epidemiological studies as reporting infrastructure develops. However, there is little incentive for governments and health systems to improve reporting without meaningful treatment options.

This analysis demonstrates a substantial disease burden exists outside of Europe, North America, and Australasia, where Vertex have largely not sought approval for CFTR modulator therapies. Even within Europe, in less affluent regions such as Eastern Europe and the Baltics ivacaftor/lumacaftor remains inaccessible years after approval [7]. With another triple combination treatment expected to advance to phase three trials this year [30], access to ivacaftor/tezacaftor/elexacaftor could set a precedent for future therapies. Yet the drug is expected to remain under patent until 2037 (Table 1). Therefore it seems that without intervention, it will remain out of reach for patients outside of the world's richest countries.

5. Conclusion

A significant patient burden exists for CF in countries where disease-modifying drugs are not available. Lack of data and systemic underdiagnosis in LMICs means these figures are likely underestimates. Urgent action is needed to improve rates of diagnosis and treatment for CF, to ensure a higher percentage of patients receive the most effective triple combination treatment, and to prevent a widening of the disparities between CF patients in HICs and LMICs.

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Data sharing statement

All data used in this study can be found in the manuscript and supplementary materials but may also be available from the corresponding author, upon reasonable request.

Declarations of Competing Interest

None.

CRediT authorship contribution statement

Jonathan Guo: Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Anna Garratt:** Writing – review & editing. **Andrew Hill:** Conceptualization, Methodology, Writing – review & editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.01.009.

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