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Global status of essential medicine selection: a systematic comparison of national essential medicine lists with recommendations by WHO

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Title:

Global status of essential medicine selection: a systematic comparison of national essential medicine lists with recommendations by WHO

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18 **Keywords**

19 Drugs, Essential; universal health insurance; insurance coverage; World Health Organization;
20 Health Expenditures
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Abstract

Objectives

Examining the availability of essential medicines is a necessary step to monitor country-level progress towards universal health coverage. We compared the 2017 essential medicine lists of 137 countries to the WHO Model List to assess differences by drug class and country setting.

Methods

We extracted all medicines prioritized at country level from most recently available national essential medicine lists (EMLs) and compared each national EML with the 2017 WHO Model List of Essential Medicines (MLEM) as the reference standard. We assess EMLs by WHO region and for different types of medicine subgroups (e.g., cancer, anti-infectives, cardiac, psychiatric and anesthesia medicines) using within second-level ATC drug classes.

Results

We included 406 medicines from WHO's 2017 MLEM to compare to 137 national EMLs current. We found a median of 315 (range from 44 to 983) medicines listed on national EMLs. The global median F1 score was 0.59 (IQR 0.47-0.70, maximum possible score indicating alignment with MLEM is 1). The F1 score was the highest (i.e. most similar to MLEM) in the South-East Asia region and the lowest in the European region (i.e. most dissimilar to MLEM). The F1 score was highest for stomatological preparations (median: 1.00), gynecological – anti-infectives and antiseptics (median: 1.00), and medicated dressings (median: 1.00), and lowest for 9 anatomical or pharmacological groups (median: 0.00 e.g. treatments for bone diseases, digestive enzymes).

Conclusions

Most countries are expected to improve their national health coverage by 2030 offering access to essential medicines, but our results revealed substantial gaps in selection of medicines at the national level compared to those by WHO as essential on a global level. It is crucial that

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3 governments consider investing in those effective medicines that are now neglected and
4 continue monitoring progress towards essential medicine access as part of universal health
5 coverage.
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12 ***Strengths and limitations of this study***
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- 14 • We present a novel data science statistical approach using the F1 statistic, not yet
15 extensively used in the health sciences field to assess the proximity of national EMLs to
16 the MLEM.
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- 18 • We present complex visualizations to support deeper understanding of national EMLs by
19 country, WHO region and drug class.
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- 21 • A limitation of this study including the subjectivity of drug class coding and
22 heterogeneity in year of listing in national EMLs.
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Background

Essential medicine lists (EMLs) are critical to prioritizing evidence-based interventions that people around the world should have access to, and governments have to work to fund. Since 1977, WHO has updated the Model List of Essential Medicines (MLEM) every two years.^{1,2} The MLEM, which includes all medicines that are considered necessary for all health systems, provides guidance to governments, health facilities and procurers on which medicines are the best value in terms of benefits for individuals and communities.^{1,2} Countries, regardless of development and resource level, can base their own national lists on the MLEM.³ Because the adoption of the MLEM offers clues on that availability of effective treatments at country levels and the amount of waste related to medicines with limited value, it is a key tool for achieving universal health coverage. Focusing on a finite list of essential medicines represents an opportunity to limit the continued increases in country care expenditures. While few items in the MLEM are highly priced, listing is the first necessary step to activate virtuous policies targeting drug prices.⁴ For these reasons, the list is primarily targeted at public policymakers in member states. However, it is of interest to several target audiences, including the general public, healthcare professionals, managers working in health facilities (eg, hospitals) or regional policymakers (e.g., at the level of districts).

Examining the availability of essential medicines and associated diseases at the country level is a necessary step to follow country-level progress towards universal health coverage (UHC). In a previous study, we measure 2017 baseline of national EMLs, and analyse global attainment as compared to essential medicines recommended by 2017 WHO MLEM.⁵ In the present study, we take this analysis further to explore attainment of essential medicines listing coverage at the level of individual drug class, presenting trends and substantial deviations by WHO region and drug class. Our hope is that such stock-taking informs discussion on how countries can improve the selection of categories of medicines for their populations and how WHO could better support member states in identifying medicines that are more effective than others within these categories.

Methods

Using the WHO Global Essential Medicines database⁶, we extracted all medicines prioritized at country level from the most recently available EM national lists. The full methods of extraction are described elsewhere.⁵ The database contains the absolute majority of listed items in MLEM, with few omissions (e.g. condoms, blood and its derivatives) which were excluded as not pertinent for the present study, as they are often outside the remit of medicine selection national authorities.

We conducted this analysis comparing national EMLs to the WHO Model List of Essential Medicine (MLEM) by applying concepts of test accuracy, where the national EML was the index tests and the MLEM the reference standard. We considered a true positive to be a medicine listed on a national EML that is also listed on the MLEM. In the context of NEMs, the definition of true negatives is somewhat arbitrary, as it may well include all medicines available in some markets that are not listed on the MLEM. Using a conservative approach, we considered all of the possible medicines that are not listed by the MLEM to be true negatives. The list and number of true negative medicines was derived from all medicines listed on any NEML that are not on the MLEM. A false positive was a medicine listed on a national EML that is not listed on the MLEM and a false negative was a medicine listed on the MLEM but not listed on a national EML. Sensitivity (also called true positive rate or recall) was defined as the proportion of medicines on a national EML out of all medicines recommended by the MLEM, and false positive rate as the proportion of medicines on a national EML out of all possible medicines listed by any national EML or the MLEM globally.

Firstly, we estimate differences between the reference standard and index tests using the true positive rate (sensitivity) and false positive rate (1-specificity). We generated a plot of the sensitivity against the false positive rate for all medicines included in the national EMLs

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3 compared to the MLEM. The analysis and relative plot define which countries are associated
4 with optimal medicine selection and which one are at risk of hazardous selection, similarly to a
5 Receiver Operator Characteristic (ROC) curve but without thresholds for test cut-off values.
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10 **Figure 1.** Defining sensitivity and precision in the context of the medicines on national EMLs,
11 visual diagram adapted from Wikipedia.⁷
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15 Secondly, we conducted an analysis based on a harmonic mean (i.e. F1 score), of the sensitivity
16 and precision (also called positive predictive value) as a single measure of performance. The F1
17 score (described in visual format in figure 1) is a well-established single measure of
18 performance.⁸ Here we use it as a single measure of performance of the national list for
19 positive list entries, with its best value at 1, and worst value at 0. In this context the
20 mathematical property of the harmonic mean tends to give more weight to countries with
21 shortest lists (which often will have better sensitivity and precision), as opposed to the
22 arithmetic mean, which is more impacted by countries with large listings of medicine. The
23 advantage of the F1 score, is that it does not incorporate true negatives, as is done in the false
24 positive rate calculation. For this reason, the F1 score has been often used in health data
25 science fields, such as in the study of machine learning models trained on electronic medical
26 records.⁹
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38 We performed analyses in Python, version 3.6.5 (Python Software Foundation) and Pandas
39 library. We prepared figures in Seaborn (doi: 10.5281/zenodo.592845) and Tableau (Seattle,
40 Washington, 2019.1). The dataset for this analysis is available in an interactive dashboard at:
41 <http://essentialmeds.org/>. We include graphical representation the ROC plot of sensitivity
42 against 1 – specificity. We also present the box-and-whisker plot of the true positive rate and F1
43 statistic for core (i.e. ambulatory or community-based medicines) and complementary (i.e.
44 specialty or hospital-based medicines) lists, by WHO region, and by drug anatomical therapeutic
45 class (ATC) level 2 categorization of medicines.¹⁰ Finally, we present a heat map of the F1
46 statistic by ATC level 2 class and country.
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Results

There were 425 entries on the WHO's 2017 MLEM, of which we included 406 medicines excluding certain MLEM entries that are not per se medicines (e.g. devices such as condoms). National EMLs had a median of 315 medications listed (IQR 268-421; range 44-983). There were 2049 medicines in total identified. Differences between the national EMLs and the MLEM varied by drug class and WHO region.

National EMLs had a median true positive rate (sensitivity) of 54.5% (IQR 47.2%-63.3%) and a median false positive rate of 5.6% (IQR 3.7%-11.1%). The true positive rate was the highest in the Pakistan EML (84.5%, 344 true positive medicines) and the lowest in the Cambodia EML (8.6%, 35 true positive medicines). The false positive rate was the highest for the Slovakia EML (41.8%, 694 false positive medicines) and the lowest in both Somalia and Cambodia EMLs (0.5%, 9 false positive medicines). That means, that in Slovakia 41.8% of medicines on the EML were not on the MEML but only 0.5% in Cambodia were not on the EML.

Results of the true positive rate (sensitivity) and false positive rate (1 - specificity) for each national EML in relation to the MLEM are presented in figure 2. National EMLs in the top left of the plot (e.g. Pakistan) have the highest sensitivity and lowest false positive rate. Countries such as Cambodia and Angola, bottom left of the plot, have a low false positive rate by also a low sensitivity, while countries such as Portugal, Czech Republic, Tunisia and Romania, top right of the plot, have higher sensitivity, but also high false positive rates. As expected, the visual inspection of the plot shows a general trend to increasing false positive rate with increasing sensitivity, i.e. the more a country lists the more it diverges from the MEML. However, this trend does not apply to several countries, including Pakistan, which stands as an outlier with a high sensitivity and low false positive rate, and countries such as Algeria, Bulgaria and Poland, with a relatively low true positive rate and a higher false positive rate, i.e. their lists only marginally overlap with WHO recommended options. Assessing figure 2 for colour denoting WHO regions, there is a trend towards a lower false positive rate and lower true positive rate for Africa, South-East Asia and the Western Pacific.

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5 Our analysis of the TPR for core and complementary MLEM medicines, presented in figure 3,
6 demonstrates substantial variation by WHO region. TPR is higher for the core essential
7 medicines in every WHO region. While Eastern Mediterranean, Europe, and the Americas have
8 a smaller difference between the sensitivity of core and complementary essential medicines,
9 Africa, South East Asia and Western Pacific have large differences indicating that many
10 complementary essential medicines often used in secondary care institutions are not being
11 listed in these regions.
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20 The global median F1 score of the national EMLs in reference to the MLEM was 0.59 (IQR 0.12).
21 The national EML with the highest F1 score, denoting closest alignment to the MLEM, was
22 Pakistan (0.88) and the lowest F1 score, denoting greatest deviation from the MLEM, was
23 Cambodia (0.16). In our analysis by WHO region, as we present in table 1 and in a box-and-
24 whisker plot in figure 4, shows that the F1 score was the highest in the South-East Asia, and the
25 lowest in the Europe region. The variability of the F1 score was the highest in Europe region and
26 the lowest in the Americas, indicating similar selection patterns in the region.
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34 We present our analysis of the F1 statistic by ATC second-level class in table 2, box-and-whisker
35 plot in figure 5, and in heat map format by national EML in figure 6. The F1 score was the
36 highest for A01 – stomatological preparations (caries prophylactic agents [e.g. sodium
37 fluoride], anti-infectives and antiseptics [e.g. metronidazole] for local oral treatment and
38 corticosteroids for local oral treatments; median 1.00, IQR 0.52), D09 – medicated dressings
39 (e.g. chlorhexidine, povidone iodine; median 1.00, IQR 0.00), and G01 – gynecological
40 anti-infectives and antiseptics (antibiotics, imidazole derivatives [e.g. nystatin], corticosteroids;
41 median 1.00, IQR 0.33) and 0.00 for a number of categories, including medicines with
42 controversial therapeutic roles such as treatments for bone diseases and digestive enzymes. For
43 certain medicine classes, including D09 – medicated dressings there is a high F1 (F1 median
44 1.00) and low IQR (F1 IQR 0.00). For other classes, including D07 – corticosteroids,
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3 dermatological preparations there is a moderate median F1 (F1 median 0.67), yet a high IQR (F1
4 IQR 0.60) denoting significant within class variability of the F1 score.
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8 **Discussion**

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10 In this study, we have found substantial variability in listing between national EML and the
11 MLEM across therapeutic classes and WHO regions. This suggests limited interest in or
12 difficulties in co-ordinating medicine prioritization and a high risk of waste of health system
13 resources from low value choices. In the context of efforts towards UHC, achieving value in
14 medicine investment, through a focus on essential medicines, is a critical approach.
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21 In 2017, we collected and analysed all national EMLs to measure if they align with those
22 medicines recommended by WHO.⁵ The number and complexity of national documents
23 supporting listed medicines suggest that countries invested a significant effort in prioritising
24 medicines. However, this amount of energy resulted in a very heterogenous scenario, with
25 countries making inconsistent selection choices, irrespective of their average income. We
26 expanded the analyses to evaluate community and hospital-based medicines and
27 pharmacological class across WHO world regions. Most countries are already selecting primary
28 care and infectious disease medicines privileging those items that ensure best returns in terms
29 of health, whereas selection of specialty or hospital-based medicines are in need of major
30 improvements to broaden coverage of relevant diseases targeted by these medicines.
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42 For many years, the WHO Model List has been viewed by some as including mostly medicines
43 for infectious disease syndromes and off-patent medicines, and as being applicable only to
44 middle-income countries or resource-constrained settings.¹¹ This has never been true as the List
45 always selected medicines relevant to any world region. In recent years, the MLEM has updated
46 and expanded its sections on chronic and non-communicable diseases, including cancer, and
47 autoimmune conditions, to reflect shifting global patterns of disease burden and the ageing
48 population.¹¹ Since 2013 the number of patented agents on the MLEM has been stable,
49 oscillating between 5% and 10% of all listed medicines.¹² The availability of targeted and
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3 biotech-based medicines (e.g. biologics such as trastuzumab for breast cancer), that typically
4 have relatively high costs, is reinforcing the global role of the Model List as a guide of a limited
5 number of highly effective medicines. The problem might not be with few high priced, highly
6 effective medicines but with the plethora of highly priced marginally or non-effective items,
7 which seems to be pervasive in several countries as identified in this analysis.
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14 Most countries are expected to improve their national health coverage by 2030 offering access
15 to a higher number of essential medicines, although our results revealed substantial gaps in
16 which medicines are selected at and beyond the national level. It is crucial that governments
17 invest in those effective medicines that are now neglected and continue to monitor progress on
18 the promise of universal health coverage, particularly for therapeutic classes with a low F1
19 statistic including blood substitutes, antihistamines for systemic use, and medicines for
20 treatment of bone diseases. It is worth noting that in the bone disease group the MLEM makes
21 highly selective recommendations, including injectable zoledronic acid treatment for
22 malignancy-related bone disease. Efforts to examine and explain areas where large range in the
23 F1 statistic exist are important to identify opportunities to better align the MLEM and national
24 EMLs.
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36 There are several potential interpretations of findings related to misalignment of national EMLs
37 and the MLEM. It is possible that the WHO List either does not make the selection at the right
38 time, anticipating or postponing medicine recommendations when countries do not
39 contemplate or have already made their decisions, or that it prioritises medicines that are of
40 less priority or not considered at country level. Another and perhaps more salient explanation
41 for the misalignment is that the rationale for essential medicines selection might not be
42 efficiently disseminated to countries. Relatively little attention has been given by WHO to its
43 role and responsibility related to effective dissemination of its rigorous evaluation of EMs to
44 date. Since 1977, recommendations of the Expert Committee are presented in the Technical
45 Report Series, a report of the EML which summaries the decisions only of those medicines for
46 which an application was presented.¹ There is, however, not yet a repository of all decisions
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3 made by the Committees over time. We are in the process of developing this repository. This
4 means that member states cannot easily retrieve, appraise, and interpret the evidence used for
5 developing the List. Progress in the way that WHO disseminates MLEM to member states,
6 including the use of the electronic list now available on essentialmeds.org, and in how it
7 supports member states in their efforts to adapt and implement MLEM, will require strong
8 leadership.
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16 The second potential interpretation is that the process to develop national EM lists at a country
17 level in certain countries is less restrictive, or more apt to select medicines, than that of WHO
18 and responds more to the pressure of the market to list additional items. Alternatively, when
19 member states adapt global recommendations that take into account local needs, conditions,
20 resources, costs, and values, the local adaptation may have far reaching consequences,
21 resulting in listing different medicines. This requires exploring how countries undertake the
22 local list-development processes, ensuring that the process is transparent, and differences
23 between the MLEM and national EM lists are justified.³ However, many countries do not clearly
24 report on how they use the MLEM to inform the development of their own national EMLs.
25 Decisions and methods rely heavily on local EM committees that rarely present in detail reasons
26 beyond listing.
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38 *Strengths*

39 This paper presents a novel approach for a single score, the F1 statistic, to assess the proximity
40 of national EMLs to the MLEM. We propose that this statistic, broadly utilized in the data
41 science field, could be more utilized in the health sciences field. We have utilized a large
42 database to explore a previously under researched topic, the listing of medicines on essential
43 medicine lists. Furthermore, we have presented analyses and visualizations to assess a broad
44 range of medicine classes for a large number of countries. This exploratory analysis also
45 presents trends that can be further analysed in subsequent research work.
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54 *Limitations*

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3 There are limitations to this present work. Limitations of the database utilized, including
4 heterogenous years of national EML listing, and subjectivity of ATC coding in the database are
5 discussed elsewhere.^{5 13} With respect to the years of listing, in extraction of national EMLs for
6 the development of this database, we used the most recently available EML, which for some
7 countries is now quite out of date. For example, the EML for Gambia that was most recently
8 available for update and inclusion in the GEM database was from 2001. As such, there may be
9 limitations in comparing to the 2017 MLEM due to evolution of the included medicines.
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16 17 18 *Implications for Policy*

19 Our analysis provides evidence for improving the transparency around decisions to include
20 medicines on essential medicine lists. Some degree of variability is expected to account for
21 contextualization based on local epidemiology or resources. However, the vast differences
22 observed between different EMLs, and the significant variability within WHO regions, suggest
23 that further transparency and consistency is necessary. For areas where we have indicated
24 there are significant deviations, reflected by a low F1 statistic, there is a need to explore at a
25 country and medicine level whether these are important and countries may wish to reconsider
26 whether they should be listing missed medicines or reconsidering medicines not listed by the
27 MLEM or many other countries.
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38 *Implications for Research*

39 Future research should explore the differences observed by groupings of medication class,
40 WHO regions, and core vs complementary medicine listings. Analysis of specific medication
41 differences within these groups will allow increased understanding of the significance and
42 importance of these differences. Analyses over time, which we are currently conducting and
43 will be available on the website (essentialmeds.org) will allow an understanding of how older
44 national EMLs compare to the historical MLEM.
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3 Our research also highlights the importance of research into the availability of medicines from
4 essential medicine lists. We utilise official listings, but our understanding of implementation of
5 these lists to support access on the ground is still limited and further research required.^{14 15}
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10 Methodologically, we have utilised innovative methods including the ROC and F1 statistic that
11 should be considered for future research on essential medicines. We propose that the F1
12 statistic be considered in analyses of essential medicine listings in relation to the WHO MLEM,
13 due to its ability to present a single measure in relation to the MLEM.
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19 Research should also assess divergences from the EML in the context of contextualization. The
20 WHO has always maintained that the EML should be contextualized to country context. An
21 example of appropriate contextualization would include differing local disease burden. It is not
22 yet known what constitutes appropriate contextualization of the list, and how this differs for
23 different medication classes. Research assessing divergence by drug class in the context of
24 disease burden would be helpful to explore divergence further.
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31 32 **Conclusions**

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34 This work highlights divergence in EML listing in countries that are particularly pronounced for
35 certain geographies, medication classes, and the MLEM complementary medicine listings.
36 Increased attention is needed to EMLs as countries work towards achieving universal health
37 coverage. Lists of medicines that should be accessible and covered, and that constitute the
38 most essential medicines, are important to this endeavour. This work enhances understanding
39 of medicine listings and highlights the importance of increasing the transparency of decisions to
40 add or remove medicines from national essential medicine lists. We hope increased
41 transparency will translate into better lists, and better access to essential medicines.
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50 51 **Author Contributions**

52 TP, AN, and LM contributed to the conceptualization of the paper. TP, RBT and AN analysed the
53 data. NP coordinated the development of the WHO Global Essential Medicines database. LM is a
54 staff member of the Secretariat of the Expert Committee on the Selection and Use of Essential
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3 Medicines and an employee of the World Health Organization, Geneva, Switzerland. NM was the
4 Secretary of the Expert Committee on the Selection and Use of Essential Medicines between 2015
5 and 2020 and an employee of the World Health Organization, Geneva, Switzerland, at the time
6 of the writing of this paper. GC was the chair of the 2019 EML Expert Committee and supported
7 in part by an NIHR Professorship. HJS contributed to early conceptualization, interpretation and
8 writing. He is the co-director of the WHO Collaborating Centre on Infectious Diseases, Research
9 Methods and Recommendations. All authors contributed to the article and approved the
10 submitted version.
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19 **Conflict of Interest**

20 The authors declare that they have no known competing financial interests or personal
21 relationships that could have appeared to influence the work reported in this paper.
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25 **Patient and Public Involvement**

26 Patients and Public were not specifically involved in the conduct of this research. However,
27 essential medicine listing authorities, such as the WHO have extensive public involvement
28 strategies.
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34 **Ethics Approval**

35 This study utilized only data on essential medicines available in the public domain. Therefore,
36 ethics review was not applicable.
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3 **Figure 2.** Essential Medicine List Receiver Operator Curve (Sensitivity vs. 1 – Specificity)
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6 **Description:** in this figure we present the sensitivity (true positive rate) plotted against 1 –
7 specificity (false positive rate). Circles represent each national EML and circle size represents
8 the total number of medicines listed. Circle colour represents WHO region. National EMLs in
9 the top left of the plot have the highest true positive rate and lowest false positive rate. Many
10 outliers exist, however, this plot demonstrates a general trend to increasing false positive rate
11 with increasing true positive rate.
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3 **Figure 3.** Box and Whisker Plot of True Positive Rate for Core and Complementary EML by WHO
4 Region.
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9 **Description:** this figure demonstrates the median, min, max, and interquartile range, in a box-
10 and-whisker plot for the true positive rates of core and complementary essential medicines by
11 WHO region. True positive rates are higher for the core essential medicines in every WHO
12 region. While Eastern Mediterranean, Europe and the Americas have a smaller difference
13 between the true positive rates of core and complementary essential medicines, Africa, South
14 East Asia and Western Pacific have large differences indicating that many complementary
15 essential medicines are not being listed in these regions.
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3 **Figure 4.** Box and Whisker Plot of F1 Statistic by WHO Region.
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8 **Description:** this figure demonstrates the median, min, max, and interquartile range, in a box-
9 and-whisker plot for F1 statistic for each WHO region. This figure demonstrates the lowest
10 median F1 statistic for Europe (0.49) and the highest for South-East Asia (0.64). As a marker of
11 within region variability, Europe has the largest inter-quartile range (0.16), and the Americas
12 demonstrates the lowest (0.05).
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3 **Figure 5.** Box and Whisker Plot of F1 statistic for all national Essential Medicine Lists by ATC level 2 drug class.
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8 **Description:** this figure demonstrates the median, min, max, and interquartile range, in a box-and-whisker plot for the F1 statistic by
9 ATC level 2 drug class. The colours present level 1 groupings of drug class. For certain drug classes, including A11 – vitamins and B03
10 – antianemic preparations, there is a high median F1 and low IQR. For other classes, including D04 - antipruritics, D11 – other
11 dermatological preparations, H04 – pancreatic hormones, the interquartile range of the F1 statistic ranges from 0 to 1.
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3 **Figure 6.** Heat Map of F1 Statistic by National EML List and ATC Drug Class (alternative presentations provided).
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6 **Description:** this figure demonstrates a heat map of the F1 statistic by drug class for each national EML, grouped by WHO region. As
7 is demonstrated, there is substantial variation in the F1 statistic by national EML and by drug class.
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Table 1. F1 statistic median by WHO region for all medications on model EML compared to national EML.

WHO Region	F1 median	F1 iqr
Africa	0.62	0.07
Americas	0.60	0.05
Eastern Mediterranean	0.57	0.13
European	0.49	0.16
South-East Asia	0.63	0.07
Western Pacific	0.51	0.10

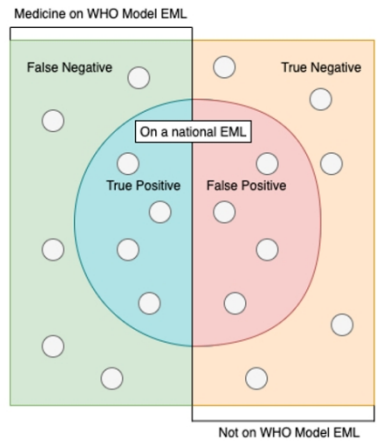
Table 2. F1 statistic median by ATC medication category for Model EML compared to national EML.

ATC & Name	F1 median	F1 iqr
A01 STOMATOLOGICAL PREPARATIONS	1.00	0.52
D09 MEDICATED DRESSINGS	1.00	0.00
G01 GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	1.00	0.33
A11 VITAMINS	0.80	0.15
A12 MINERAL SUPPLEMENTS	0.80	0.24
C03 DIURETICS	0.80	0.19
A03 DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	0.80	0.31
N01 ANESTHETICS	0.77	0.27
B03 ANTIANEMIC PREPARATIONS	0.75	0.11
C08 CALCIUM CHANNEL BLOCKERS	0.75	0.26
H02 CORTICOSTEROIDS FOR SYSTEMIC USE	0.75	0.22
N03 ANTIEPILEPTICS	0.73	0.18
C07 BETA BLOCKING AGENTS	0.72	0.13
J07 VACCINES	0.69	0.25
J01 ANTIBACTERIALS FOR SYSTEMIC USE	0.67	0.14
C01 CARDIAC THERAPY	0.67	0.21
S01 OPHTHALMOLOGICALS	0.67	0.22
B01 ANTITHROMBOTIC AGENTS	0.67	0.22
L04 IMMUNOSUPPRESSANTS	0.67	0.30
C02 ANTIHYPERTENSIVES	0.67	0.36
H03 THYROID THERAPY	0.67	0.29
C05 VASOPROTECTIVES	0.67	0.40
D07 CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	0.67	0.60
H01 PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES	0.67	0.22
M04 ANTIGOUT PREPARATIONS	0.67	0.33
P03 ECTOPARASITICIDES, INCL. SCABICIDES, INSECTICIDES AND REPELLENTS	0.67	0.51

N05 PSYCHOLEPTICS	0.63	0.22
J04 ANTIMYCOBACTERIALS	0.62	0.17
L01 ANTINEOPLASTIC AGENTS	0.62	0.38
A02 DRUGS FOR ACID RELATED DISORDERS	0.60	0.31
A07 ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	0.60	0.21
A10 DRUGS USED IN DIABETES	0.60	0.17
D01 ANTIFUNGALS FOR DERMATOLOGICAL USE	0.60	0.17
D06 ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	0.60	0.25
J06 IMMUNE SERA AND IMMUNOGLOBULINS	0.60	0.27
N02 ANALGESICS	0.59	0.21
A06 DRUGS FOR CONSTIPATION	0.57	0.17
R03 DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.57	0.17
J02 ANTIMYCOTICS FOR SYSTEMIC USE	0.57	0.18
N04 ANTI-PARKINSON DRUGS	0.57	0.31
R05 COUGH AND COLD PREPARATIONS	0.57	0.35
B02 ANTIHEMORRHAGICS	0.54	0.33
G03 SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	0.52	0.17
N06 PSYCHOANALEPTICS	0.50	0.28
P02 ANTHELMINTICS	0.50	0.35
M03 MUSCLE RELAXANTS	0.50	0.33
N07 OTHER NERVOUS SYSTEM DRUGS	0.50	0.27
A04 ANTIEMETICS AND ANTINAUSEANTS	0.50	0.67
D10 ANTI-ACNE PREPARATIONS	0.50	0.67
G02 OTHER GYNECOLOGICALS	0.50	0.80
J05 ANTIVIRALS FOR SYSTEMIC USE	0.49	0.17
V03 ALL OTHER THERAPEUTIC PRODUCTS	0.44	0.27
C09 AGENTS ACTING ON THE RENIN- ANGIOTENSIN SYSTEM	0.44	0.43
M01 ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.44	0.26
P01 ANTIPROTOZOALS	0.41	0.29

L02 ENDOCRINE THERAPY	0.40	0.15
L03 IMMUNOSTIMULANTS	0.40	0.17
R01 NASAL PREPARATIONS	0.40	0.60
C10 LIPID MODIFYING AGENTS	0.22	0.67
R06 ANTIHISTAMINES FOR SYSTEMIC USE	0.17	0.29
A09 DIGESTIVES, INCL. ENZYMES	0.00	0.50
B05 BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	0.00	0.50
D02 EMOLLIENTS AND PROTECTIVES	0.00	0.50
D04 ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	0.00	1.00
D05 ANTIPSORIATICS	0.00	0.67
D08 ANTISEPTICS AND DISINFECTANTS	0.00	0.00
D11 OTHER DERMATOLOGICAL PREPARATIONS	0.00	1.00
H04 PANCREATIC HORMONES	0.00	1.00
M05 DRUGS FOR TREATMENT OF BONE DISEASES	0.00	0.26

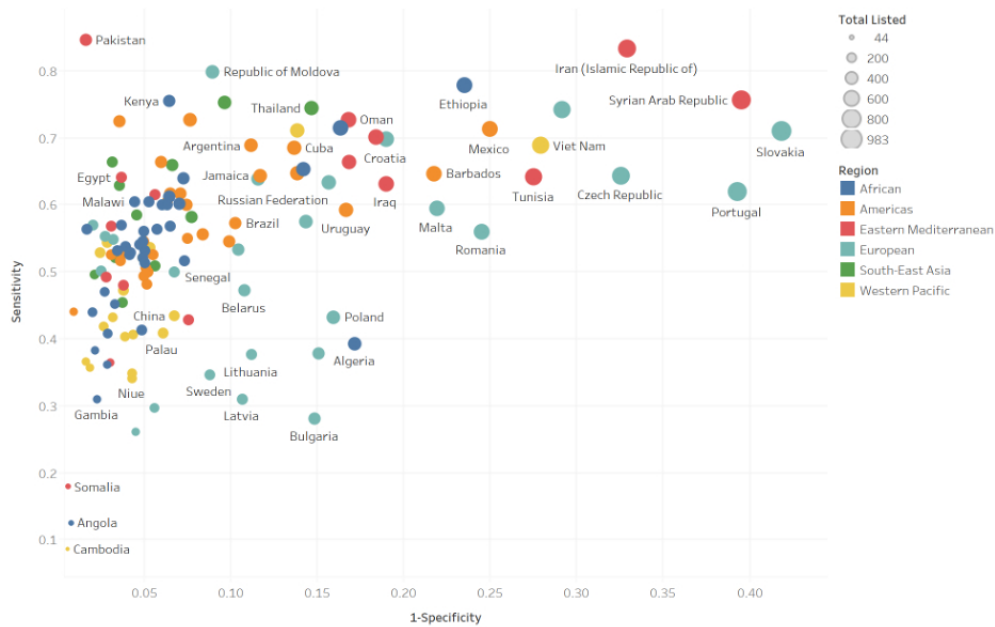
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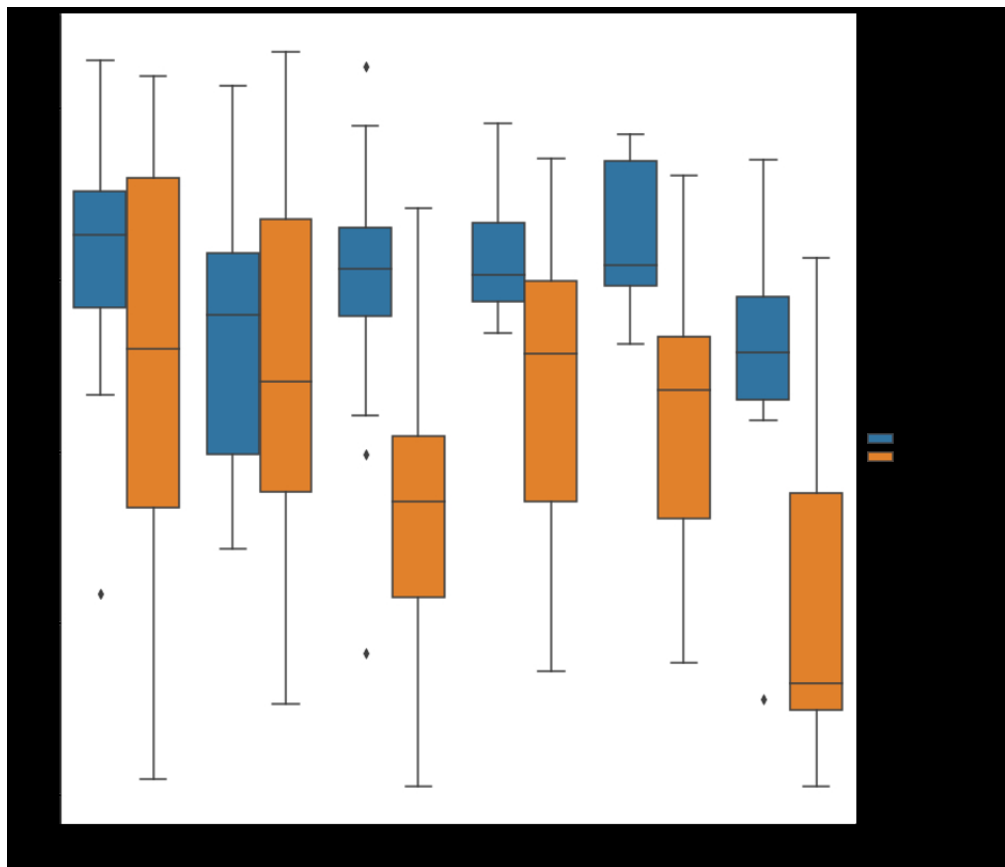
Precision = $\frac{\text{True Positive}}{\text{True Positive} + \text{False Positive}}$

Recall = $\frac{\text{True Positive}}{\text{True Positive} + \text{False Negative}}$
(Sensitivity)

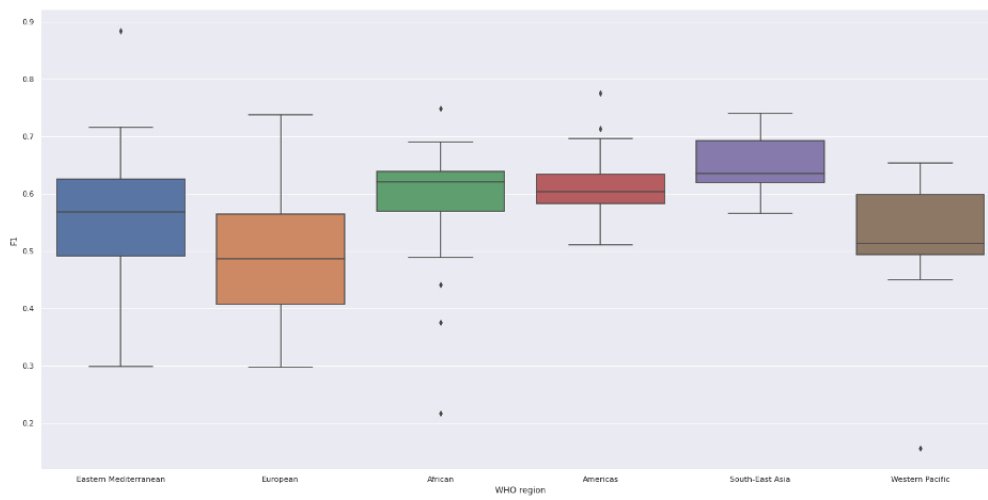
EML Receiver Operator Curve



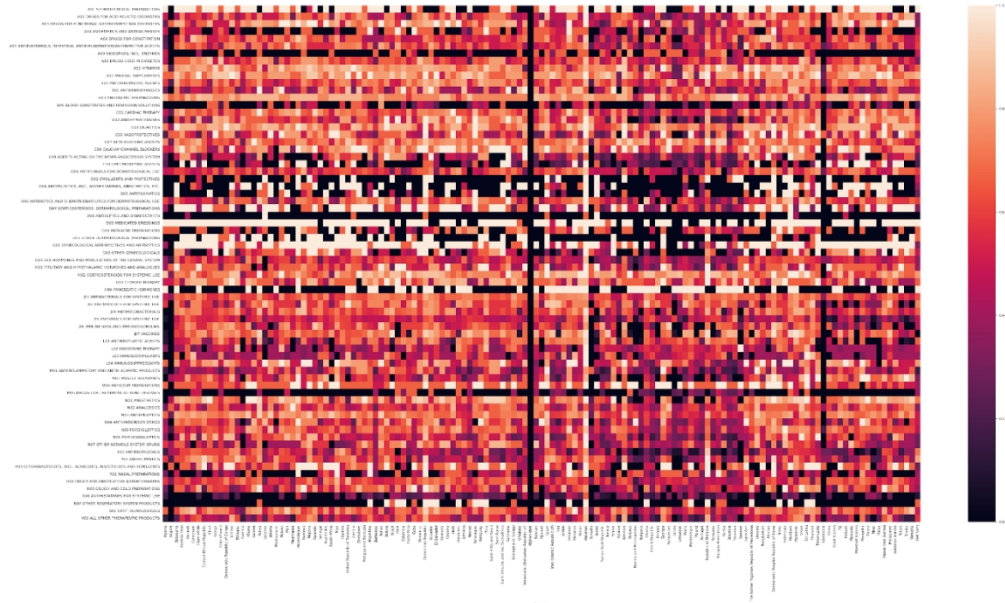
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Global status of essential medicine selection: a systematic comparison of national essential medicine lists with recommendations by WHO

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Title:

Global status of essential medicine selection: a systematic comparison of national essential medicine lists with recommendations by WHO

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Keywords

Drugs, Essential; universal health insurance; insurance coverage; World Health Organization;
Health Expenditures

61 **Abstract**

63 **Objectives**

64 Examining the availability of essential medicines is a necessary step to monitor country-level
65 progress towards universal health coverage. We compared the 2017 essential medicine lists of
66 137 countries to the WHO Model List to assess differences by drug class and country setting.

68 **Methods**

69 We extracted all medicines prioritized at country level from most recently available national
70 essential medicine lists (EMLs) and compared each national EML with the 2017 WHO Model
71 List of Essential Medicines (MLEM) as the reference standard. We assess EMLs by WHO
72 region and for different types of medicine subgroups (e.g., cancer, anti-infectives, cardiac,
73 psychiatric and anesthesia medicines) using within second-level ATC drug classes.

75 **Results**

76 We included 406 medicines from WHO's 2017 MLEM to compare to 137 national EMLs
77 current. We found a median of 315 (range from 44 to 983) medicines listed on national EMLs.
78 The global median F1 score was 0.59 (IQR 0.47-0.70, maximum possible score indicating
79 alignment with MLEM is 1). The F1 score was the highest (i.e. most similar to MLEM) in the
80 South-East Asia region and the lowest in the European region (i.e. most dissimilar to MLEM).
81 The F1 score was highest for stomatological preparations (median: 1.00), gynecological – anti-
82 infectives and antiseptics (median: 1.00), and medicated dressings (median: 1.00), and lowest for
83 9 anatomical or pharmacological groups (median: 0.00 e.g. treatments for bone diseases,
84 digestive enzymes).

86 **Conclusions**

87 Most countries are expected to improve their national health coverage by 2030 offering access to
88 essential medicines, but our results revealed substantial gaps in selection of medicines at the
89 national level compared to those by WHO as essential on a global level. It is crucial that
90 governments consider investing in those effective medicines that are now neglected and continue
91 monitoring progress towards essential medicine access as part of universal health coverage.

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Strengths and limitations of this study

- We present a novel data science statistical approach using the F1 statistic, not yet extensively used in the health sciences field to assess the proximity of national EMLs to the MLEM.
- We present complex visualizations to support deeper understanding of national EMLs by country, WHO region and drug class.
- A limitation of this study including the subjectivity of drug class coding and heterogeneity in year of listing in national EMLs.

103 **Background**

104

105 Essential medicine lists (EMLs) are critical to prioritizing evidence-based interventions that
106 people around the world should have access to, and governments have to work to fund. The
107 adoption of these priority tools into public policy could generate important savings by
108 concentrating competition on a smaller number of medicines and better negotiating medication
109 prices. In some settings, EMLs may drive medicine procurement decisions and in other settings
110 national insurers will utilize EMLs for reimbursement decisions. Approximately 137 countries
111 out of 194 World Health Organization (WHO) member states have formal national EMLs
112 (70.6%).¹ Since 1977, the WHO has updated the Model List of Essential Medicines (MLEM)
113 every two years.^{2,3} The MLEM, which includes all medicines that are considered necessary for
114 all health systems, provides guidance to governments, health facilities and procurers on which
115 medicines are the best value in terms of benefits for individuals and communities.^{2,3} Countries,
116 regardless of development and resource level, can base their own national lists on the MLEM.⁴
117 Because the adoption of the MLEM offers clues on that availability of effective treatments at
118 country levels and the amount of waste related to medicines with limited value, it is a key tool
119 for achieving universal health coverage. Focusing on a finite list of essential medicines
120 represents an opportunity to limit the continued increases in country care expenditures. While
121 few items in the MLES are highly priced, listing is the first necessary step to activate virtuous
122 policies targeting drug prices.⁵ For these reasons, the list is primarily targeted at public
123 policymakers in member states. However, it is of interest to several target audiences, including
124 the general public, healthcare professionals, managers working in health facilities (eg, hospitals)
125 or regional policymakers (e.g., at the level of districts).

126

127 Examining the availability of essential medicines and associated diseases at the country level is a
128 necessary step to follow country-level progress towards universal health coverage (UHC). In a
129 previous study, we measure 2017 baseline of national EMLs, and analyse global attainment as
130 compared to essential medicines recommended by 2017 WHO MLEM.⁶ In the present study, we
131 take this analysis further to explore attainment of essential medicines listing coverage at the level
132 of individual drug class, presenting trends and substantial deviations by WHO region and drug
133 class. In particular, we explore analysis and visualizations using a single entity, the F1 statistic to

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3 134 assess national essential medicine listings in relation to the MLEM. Our hope is that such stock-
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5 135 taking informs discussion on how countries can improve the selection of categories of medicines
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7 136 for their populations and how WHO could better support member states in identifying medicines
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9 137 that are more effective than others within these categories.

10 138

11 139 **Methods**

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13 140 Using the WHO Global Essential Medicines database ¹, we extracted all medicines prioritized at
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15 141 country level from the most recently available EM national lists. This database draws on national
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17 142 EMLs that have been included in the WHO repository and does not directly draw from WHO
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19 143 member states for the purposes of this paper. The database consists of 137 country EMLs and the
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21 144 validation and full methods of extraction are described elsewhere.⁶ The database contains the
22
23 145 absolute majority of listed items in MLEM, with few omissions (e.g. condoms, blood and its
24
25 146 derivatives), which were excluded as not pertinent for the present study, as they are often outside
26
27 147 the remit of medicine selection national authorities. The MLEM includes medicines with a
28
29 148 square box indicator, which denotes therapeutic equivalence with other medications in the same
30
31 149 class.⁶ For the purpose of this study we have assumed that for square box MLEM medicines any
32
33 150 class therapeutic equivalent alternative listed by national EMLs is a matching entry.

34 151

35 152 We conducted this analysis comparing national EMLs to the WHO Model List of Essential
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37 153 Medicine (MLEM) by applying concepts of test accuracy, where the national EML was the index
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39 154 tests and the MLEM the reference standard. We considered a true positive to be a medicine listed
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41 155 on a national EML that is also listed on the MLEM. In the context of NEMLs, the definition of
42
43 156 true negatives is somewhat arbitrary, as it may well include all medicines available in some
44
45 157 markets that are not listed on the MLEM. Using a conservative approach, we considered all of
46
47 158 the possible medicines that are not listed by the MLEM to be true negatives. The list and number
48
49 159 of true negative medicines was derived from all medicines listed on any NEML that are not on
50
51 160 the MLEM. A false positive was a medicine listed on a national EML that is not listed on the
52
53 161 MLEM and a false negative was a medicine listed on the MLEM but not listed on a national
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55 162 EML. Sensitivity (also called true positive rate or recall) was defined as the proportion of
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57 163 medicines on a national EML out of all medicines recommended by the MLEM, and false

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3 164 positive rate as the proportion of medicines on a national EML out of all possible medicines
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5 165 listed by any national EML or the MLEM globally.
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8 167 Firstly, we estimate differences between the reference standard and index tests using the true
9
10 168 positive rate, TPR, (sensitivity) and false positive rate, FPR, (1-specificity). We generated a plot
11
12 169 of the sensitivity against the false positive rate for all medicines included in the national EMLs
13
14 170 compared to the MLEM. The analysis and relative plot define which countries are associated
15
16 171 with optimal medicine selection and which one are at risk of hazardous selection, similarly to a
17 172 Receiver Operator Characteristic (ROC) curve but without thresholds for test cut-off values.
18
19 173

20 174 **Figure 1.** Defining sensitivity and precision in the context of the medicines on national EMLs,
21 175 visual diagram adapted from Wikipedia.⁷
22 176

23
24 177 Secondly, we conducted an analysis based on a harmonic mean (i.e. F1 score), of the sensitivity
25
26 178 and precision (also called positive predictive value) as a single measure of performance. The F1
27
28 179 score (described in visual format in figure 1) is a well-established single measure of
29
30 180 performance.⁸ Here we use it as a single measure of performance of the national list for positive
31
32 181 list entries, with its best value at 1, and worst value at 0. In this context the mathematical
33
34 182 property of the harmonic mean tends to give more weight to countries with shortest lists (which
35
36 183 often will have better sensitivity and precision), as opposed to the arithmetic mean, which is
37
38 184 more impacted by countries with large listings of medicine. The advantage of the F1 score, is
39
40 185 that it does not incorporate true negatives, as is done in the false positive rate calculation. For
41
42 186 this reason, the F1 score has been often used in health data science fields, such as in the study of
43
44 187 machine learning models trained on electronic medical records.⁹
45
46 188

47 189 We performed analyses in Python, version 3.6.5 (Python Software Foundation) and Pandas
48
49 190 library. We prepared figures in Seaborn (doi: 10.5281/zenodo.592845) and Tableau (Seattle,
50
51 191 Washington, 2019.1). The dataset for this analysis is available in an interactive dashboard at:
52
53 192 <http://essentialmeds.org/>.¹⁰ We include graphical representation the ROC plot of sensitivity
54
55 193 against 1 – specificity. We also present the box-and-whisker plot of the true positive rate and F1
56
57 194 statistic for core (i.e. ambulatory or community-based medicines) and complementary (i.e.
58
59 195 specialty or hospital-based medicines) lists, by WHO region, and by drug anatomical therapeutic

196 class (ATC) level 2 categorization of medicines.¹¹ Finally, we present a heat map of the F1
197 statistic by ATC level 2 class and country.

198

199 *Patient and Public Involvement*

200 Patients and Public were not specifically involved in the conduct of this research. However, the
201 MEML is a highly democratic process, in which all requests for change are published, and open
202 for public review and comment.

203

204 **Results**

205 There were 425 entries on the WHO's 2017 MLEM, of which we included 406 medicines
206 excluding certain MLEM entries that are not per se medicines (e.g. devices such as condoms).
207 National EMLs had a median of 315 medications listed (IQR 268-421; range 44-983). Further
208 descriptive analyses on the countries and medicines included are available in Persaud et al ⁶.

209 There were 2049 medicines in total identified. Differences between the national EMLs and the
210 MLEM varied by drug class and WHO region.

211

212 National EMLs had a median true positive rate (sensitivity) of 54.5% (IQR 47.2%-63.3%) and a
213 median false positive rate of 5.6% (IQR 3.7%-11.1%). The true positive rate was the highest in
214 the Pakistan EML (84.5%, 344 true positive medicines) and the lowest in the Cambodia EML
215 (8.6%, 35 true positive medicines). The false positive rate was the highest for the Slovakia EML
216 (41.8%, 694 false positive medicines) and the lowest in both Somalia and Cambodia EMLs
217 (0.5%, 9 false positive medicines). That means, that in Slovakia 41.8% of medicines on the EML
218 were not on the MEML but only 0.5% in Cambodia were not on the EML.

219

220 Results of the true positive rate (sensitivity) and false positive rate (1 - specificity) for each
221 national EML in relation to the MLEM are presented in figure 2. National EMLs in the top left
222 of the plot (e.g. Pakistan) have the highest sensitivity and lowest false positive rate. Countries
223 such as Cambodia and Angola, bottom left of the plot, have a low false positive rate by also a
224 low sensitivity, while countries such as Portugal, Czech Republic, Tunisia and Romania, top
225 right of the plot, have higher sensitivity, but also high false positive rates. As expected, the visual
226 inspection of the plot shows a general trend to increasing false positive rate with increasing

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3 227 sensitivity, i.e. the more a country lists the more it diverges from the MEML. However, this
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5 228 trend does not apply to several countries, including Pakistan, which stands as an outlier with a
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7 229 high sensitivity and low false positive rate, and countries such as Algeria, Bulgaria and Poland,
8
9 230 with a relatively low true positive rate and a higher false positive rate, i.e. their lists only
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11 231 marginally overlap with WHO recommended options. Assessing figure 2 for colour denoting
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13 232 WHO regions, there is a trend towards a lower false positive rate and lower true positive rate for
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15 233 Africa, South-East Asia and the Western Pacific.

16 234
17 235 Our analysis of the TPR for core and complementary MLEM medicines, presented in figure 3,
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19 236 demonstrates substantial variation by WHO region. TPR is higher for the core essential
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21 237 medicines in every WHO region. While Eastern Mediterranean, Europe, and the Americas have a
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23 238 smaller difference between the sensitivity of core and complementary essential medicines,
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25 239 Africa, South East Asia and Western Pacific have large differences indicating that many
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27 240 complementary essential medicines often used in secondary care institutions are not being listed
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29 241 in these regions.

30 242
31 243 The global median F1 score of the national EMLs in reference to the MLEM was 0.59 (IQR
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33 244 0.12). The national EML with the highest F1 score, denoting closest alignment to the MLEM,
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35 245 was Pakistan (0.88) and the lowest F1 score, denoting greatest deviation from the MLEM, was
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37 246 Cambodia (0.16). In our analysis by WHO region, as we present in table 1 and in a box-and-
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39 247 whisker plot in figure 4, shows that the F1 score was the highest in the South-East Asia, and the
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41 248 lowest in the Europe region. The variability of the F1 score was the highest in Europe region and
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43 249 the lowest in the Americas, indicating similar selection patterns in the region.

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45 251 We present our analysis of the F1 statistic by ATC second-level class in table 2, box-and-whisker
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47 252 plot in figure 5, and in heat map format by national EML in figure 6. The F1 score was the
48
49 253 highest for A01 – stomatological preparations (caries prophylactic agents [e.g. sodium fluoride],
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51 254 anti-infectives and antiseptics [e.g. metronidazole] for local oral treatment and corticosteroids for
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53 255 local oral treatments; median 1.00, IQR 0.52), D09 – medicated dressings (e.g. chlorhexidine,
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55 256 povidone iodine; median 1.00, IQR 0.00), and G01 – gynecological antiinfectives and antiseptics
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57 257 (antibiotics, imidazole derivatives [e.g. nystatin], corticosteroids; median 1.00, IQR 0.33) and

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3 258 0.00 for a number of categories, including medicines with controversial therapeutic roles such as
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5 259 treatments for bone diseases and digestive enzymes. For certain medicine classes, including D09
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7 260 – medicated dressings there is a high F1 (F1 median 1.00) and low IQR (F1 IQR 0.00). For other
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9 261 classes, including D07 – corticosteroids, dermatological preparations there is a moderate median
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11 262 F1 (F1 median 0.67), yet a high IQR (F1 IQR 0.60) denoting significant within class variability
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13 263 of the F1 score.
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15 265 **Discussion**

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17 266 In this study, we have found substantial variability in listing between national EML and the
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19 267 MLEM across therapeutic classes and WHO regions. This suggests limited interest in or
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21 268 difficulties in co-ordinating medicine prioritization and a high risk of waste of health system
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23 269 resources from low value choices. In the context of efforts towards UHC, achieving value in
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25 270 medicine investment, through a focus on essential medicines, is a critical approach.
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27 272 In 2017, we collected and analysed all national EMLs to measure if they align with those
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29 273 medicines recommended by WHO.⁶ The number and complexity of national documents
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31 274 supporting listed medicines suggest that countries invested a significant effort in prioritising
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33 275 medicines. However, this amount of energy resulted in a very heterogenous scenario, with
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35 276 countries making inconsistent selection choices, irrespective of their average income. We
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37 277 expanded the analyses to evaluate community and hospital-based medicines and pharmacological
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39 278 class across WHO world regions. Most countries are already selecting primary care and
40
41 279 infectious disease medicines privileging those items that ensure best returns in terms of health,
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43 280 whereas selection of specialty or hospital-based medicines are in need of major improvements to
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45 281 broaden coverage of relevant diseases targeted by these medicines.
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47 283 For many years, the WHO Model List has been viewed by some as including mostly medicines
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49 284 for infectious disease syndromes and off-patent medicines, and as being applicable only to
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51 285 middle-income countries or resource-constrained settings.¹² This has never been true as the List
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53 286 always selected medicines relevant to any world region. In recent years, the MLEM has updated
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55 287 and expanded its sections on chronic and non-communicable diseases, including cancer, and
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57 288 autoimmune conditions, to reflect shifting global patterns of disease burden and the ageing

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3 289 population.¹² Since 2013 the number of patented agents on the MLEM has been stable,
4 290 oscillating between 5% and 10% of all listed medicines.¹³ The availability of targeted and
5 291 biotech-based medicines (e.g. biologics such as trastuzumab for breast cancer), that typically
6 292 have relatively high costs, is reinforcing the global role of the Model List as a guide of a limited
7 293 number of highly effective medicines. The problem might not be with few high priced, highly
8 294 effective medicines but with the plethora of highly priced marginally or non-effective items,
9 295 which seems to be pervasive in several countries as identified in this analysis.
10 296

11 297 Most countries are expected to improve their national health coverage by 2030 offering access to
12 298 a higher number of essential medicines, although our results revealed substantial gaps in which
13 299 medicines are selected at and beyond the national level. It is crucial that governments invest in
14 300 those effective medicines that are now neglected and continue to monitor progress on the
15 301 promise of universal health coverage, particularly for therapeutic classes with a low F1 statistic
16 302 including blood substitutes, antihistamines for systemic use, and medicines for treatment of bone
17 303 diseases. It is worth noting that in the bone disease group the MLEM makes highly selective
18 304 recommendations, including injectable zoledronic acid treatment for malignancy-related bone
19 305 disease. Efforts to examine and explain areas where large range in the F1 statistic exist are
20 306 important to identify opportunities to better align the MLEM and national EMLs.
21 307

22 308 There are several potential interpretations of findings related to misalignment of national EMLs
23 309 and the MLEM. It is possible that the WHO List either does not make the selection at the right
24 310 time, anticipating or postponing medicine recommendations when countries do not contemplate
25 311 or have already made their decisions, or that it prioritises medicines that are of less priority or not
26 312 considered at country level. Another and perhaps more salient explanation for the misalignment
27 313 is that the rationale for essential medicines selection might not be efficiently disseminated to
28 314 countries. Relatively little attention has been given by WHO to its role and responsibility related
29 315 to effective dissemination of its rigorous evaluation of EMs to date. Since 1977,
30 316 recommendations of the Expert Committee are presented in the Technical Report Series, a report
31 317 of the EML which summaries the decisions only of those medicines for which an application was
32 318 presented.² There is, however, not yet a repository of all decisions made by the Committees over
33 319 time. We are in the process of developing this repository. This means that member states cannot
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3 320 easily retrieve, appraise, and interpret the evidence used for developing the List. Progress in the
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5 321 way that WHO disseminates MLEM to member states, including the use of the electronic list
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7 322 now available on essentialmeds.org, and in how it supports member states in their efforts to
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9 323 adapt and implement MLEM, will require strong leadership.

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12 325 The second potential interpretation is that the process to develop national EM lists at a country
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14 326 level in certain countries is less restrictive, or more apt to select medicines, than that of WHO
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16 327 and responds more to the pressure of the market to list additional items. Alternatively, when
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18 328 member states adapt global recommendations that take into account local needs, conditions,
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20 329 resources, costs, and values, the local adaptation may have far reaching consequences, resulting
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22 330 in listing different medicines. This requires exploring how countries undertake the local list-
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24 331 development processes, ensuring that the process is transparent, and differences between the
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26 332 MLEM and national EM lists are justified.⁴ However, many countries do not clearly report on
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28 333 how they use the MLEM to inform the development of their own national EMLs. Decisions and
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30 334 methods rely heavily on local EM committees that rarely present in detail reasons beyond listing.

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33 336 *Strengths*

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35 337 This paper presents a novel approach for a single score, the F1 statistic, to assess the proximity
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37 338 of national EMLs to the MLEM. We propose that this statistic, broadly utilized in the data
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39 339 science field, could be more utilized in the health sciences field. We have utilized a large
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41 340 database to explore a previously under researched topic, the listing of medicines on essential
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43 341 medicine lists. Furthermore, we have presented analyses and visualizations to assess a broad
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45 342 range of medicine classes for a large number of countries. This exploratory analysis also presents
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47 343 trends that can be further analysed in subsequent research work.

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49
50 345 *Limitations*

51
52 346 There are limitations to this present work. Limitations of the database utilized, including
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54 347 heterogenous years of national EML listing, and subjectivity of ATC coding in the database are
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56 348 discussed elsewhere.^{6 14} With respect to the years of listing, in extraction of national EMLs for
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58 349 the development of this database, we used the most recently available EML, which for some
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60 350 countries is now quite out of date. For example, the EML for Gambia that was most recently

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3 351 available for update and inclusion in the GEM database was from 2001. As such, there may be
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5 352 limitations in comparing to the 2017 MLEM due to evolution of the included medicines. Finally,
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7 353 our evaluation is limited to the availability of essential medicines in official government
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9 354 documents. Results can or cannot translate in availability at patient level.

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11 356 *Implications for Policy*

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13 357 Our analysis provides evidence for improving the transparency around decisions to include
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15 358 medicines on essential medicine lists. Some degree of variability is expected to account for
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17 359 contextualization based on local epidemiology or resources. However, the vast differences
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19 360 observed between different EMLs, and the significant variability within WHO regions, suggest
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21 361 that further transparency and consistency is necessary. For areas where we have indicated there
22
23 362 are significant deviations, reflected by a low F1 statistic, there is a need to explore at a country
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25 363 and medicine level whether these are important and countries may wish to reconsider whether
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27 364 they should be listing missed medicines or reconsidering medicines not listed by the MLEM or
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29 365 many other countries.

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31 367 *Implications for Research*

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33 368 Future research should explore the differences observed by groupings of medication class, WHO
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35 369 regions, and core vs complementary medicine listings. Analysis of specific medication
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37 370 differences within these groups will allow increased understanding of the significance and
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39 371 importance of these differences. Analyses over time, which we are currently conducting and will
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41 372 be available on the website (essentialmeds.org) will allow an understanding of how older
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43 373 national EMLs compare to the historical MLEM. Our research also highlights the importance of
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45 374 research into the availability of medicines from essential medicine lists. We utilise official
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47 375 listings, but our understanding of implementation of these lists to support access on the ground is
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49 376 still limited and further research required.^{15 16} Future research continue to assess medicine
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51 377 listings on NEMs by disease groups and for focused disciplinary as has been done for tobacco
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53 378 addiction, diabetes, and heart disease among other topics.¹⁷⁻¹⁹

54 379

55 380 Methodologically, we have utilised innovative methods including the ROC and F1 statistic that
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57 381 should be considered for future research on essential medicines. We propose that the F1 statistic

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3 382 be considered in analyses of essential medicine listings in relation to the WHO MLEM, due to its
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5 383 ability to present a single measure in relation to the MLEM.
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8 385 Research should also assess divergences from the EML in the context of contextualization. The
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10 386 WHO has always maintained that the EML should be contextualized to country context. An
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12 387 example of appropriate contextualization would include differing local disease burden. It is not
13
14 388 yet known what constitutes appropriate contextualization of the list, and how this differs for
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16 389 different medication classes. Research assessing divergence by drug class in the context of
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18 390 disease burden would be helpful to explore divergence further. Finally, further research is needed
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20 391 to better understand how listing on an EML translates to access policies and availability of
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22 392 medicines for patients, the ultimate goal. Simply listing medicines is not going to solve the
23
24 393 problem of scarce coverage, but it is a necessary first step to enable identification of priority
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26 394 medicines and the subsequent tracking of their availability.
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28 395

27 396 **Conclusions**

29 397 This work highlights divergence in EML listing in countries that are particularly pronounced for
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31 398 certain geographies, medication classes, and the MLEM complementary medicine listings.
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33 399 Increased attention is needed to EMLs as countries work towards achieving universal health
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35 400 coverage. Lists of medicines that should be accessible and covered, and that constitute the most
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37 401 essential medicines, are important to this endeavour. This work enhances understanding of
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39 402 medicine listings and highlights the importance of increasing the transparency of decisions to
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41 403 add or remove medicines from national essential medicine lists. We hope increased transparency
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43 404 will translate into better lists, and better access to essential medicines.
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45 405

44 406 **Contribution Statement**

46 407 TP, AN, and LM contributed to the conceptualization of the paper. TP, RBT and AN analysed the
47
48 408 data. NP coordinated the development of the WHO Global Essential Medicines database. LM is a
49
50 409 staff member of the Secretariat of the Expert Committee on the Selection and Use of Essential
51
52 410 Medicines and an employee of the World Health Organization, Geneva, Switzerland. NM was the
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54 411 Secretary of the Expert Committee on the Selection and Use of Essential Medicines between 2015
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56 412 and 2020 and an employee of the World Health Organization, Geneva, Switzerland, at the time of
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2
3 413 the writing of this paper. GC was the chair of the 2019 EML Expert Committee and supported in
4
5 414 part by an NIHR Professorship. HJS contributed to early conceptualization, interpretation and
6
7 415 writing. He is the co-director of the WHO Collaborating Centre on Infectious Diseases, Research
8
9 416 Methods and Recommendations. All authors contributed to the article and approved the submitted
10
11 417 version.

12 418

13 419 **Competing Interests**

14 420 The authors declare that they have no known competing financial interests or personal

15
16 421 relationships that could have appeared to influence the work reported in this paper.

17 422

19 423 **Ethics Approval**

20 424 This study utilized only data on essential medicines available in the public domain. Therefore,
21
22 425 ethics review was not applicable.

23 426

25 427 **Funding**

27 428 The development of this work has been possible thanks to the funding from the Universal Health

28
29 429 Coverage (UHC) Partnership [<https://www.uhpartnership.net/>], which is one of the WHO

30
31 430 largest initiatives for international cooperation for UHC and primary health care (PHC). It helps

32
33 431 deliver WHO support and technical expertise in advancing UHC with a PHC approach to 115

34
35 432 countries, through funding from the European Union (EU), the Grand Duchy of Luxembourg,

36
37 433 Irish Aid, the Government of Japan, the French Ministry for Europe and Foreign Affairs, the

38
39 434 United Kingdom – Foreign, Commonwealth & Development Office, Belgium, Canada, and

40
41 435 Germany.

42 436

43 437 **Data Sharing Statement**

44
45 438 All data used in the production of this manuscript is available on the public access website:

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47 439 <https://essentialmeds.org/>

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17 495

18 496 **Figure 2.** Essential Medicine List Receiver Operator Curve (Sensitivity vs. 1 – Specificity)
19 497

20 498 **Description:** in this figure we present the sensitivity (true positive rate) plotted against 1 –
21 499 specificity (false positive rate). Circles represent each national EML and circle size represents
22 500 the total number of medicines listed. Circle colour represents WHO region. National EMLs in
23 501 the top left of the plot have the highest true positive rate and lowest false positive rate. Many
24 502 outliers exist, however, this plot demonstrates a general trend to increasing false positive rate
25 503 with increasing true positive rate.
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3 505 **Figure 3.** Box and Whisker Plot of True Positive Rate for Core and Complementary EML by
4 506 WHO Region.

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8 510 **Description:** this figure demonstrates the median, min, max, and interquartile range, in a box-
9 511 and-whisker plot for the true positive rates of core and complementary essential medicines by
10 512 WHO region. True positive rates are higher for the core essential medicines in every WHO
11 513 region. While Eastern Mediterranean, Europe and the Americas have a smaller difference
12 514 between the true positive rates of core and complementary essential medicines, Africa, South
13 515 East Asia and Western Pacific have large differences indicating that many complementary
14 516 essential medicines are not being listed in these regions.
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3 518 **Figure 4.** Box and Whisker Plot of F1 Statistic by WHO Region.
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7 522 **Description:** this figure demonstrates the median, min, max, and interquartile range, in a box-

8 523 and-whisker plot for F1 statistic for each WHO region. This figure demonstrates the lowest

9 524 median F1 statistic for Europe (0.49) and the highest for South-East Asia (0.64). As a marker of

10 525 within region variability, Europe has the largest inter-quartile range (0.16), and the Americas

11 526 demonstrates the lowest (0.05).
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3 529 **Figure 5.** Box and Whisker Plot of F1 statistic for all national Essential Medicine Lists by ATC level 2 drug class.

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Description: this figure demonstrates the median, min, max, and interquartile range, in a box-and-whisker plot for the F1 statistic by ATC level 2 drug class. The colours present level 1 groupings of drug class. For certain drug classes, including A11 – vitamins and B03 – antianemic preparations, there is a high median F1 and low IQR. For other classes, including D04 - antipruritics, D11 – other dermatological preparations, H04 – pancreatic hormones, the interquartile range of the F1 statistic ranges from 0 to 1.

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3 537 **Figure 6.** Heat Map of F1 Statistic by National EML List and ATC Drug Class (alternative presentations provided).

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5 539 **Description:** this figure demonstrates a heat map of the F1 statistic by drug class for each national EML, grouped by WHO region. As
6 540 is demonstrated, there is substantial variation in the F1 statistic by national EML and by drug class.
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3 **Table 1.** F1 statistic median by WHO region for all medications on model EML compared to
4 national EML.
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Region	# of National EMLs	f1 median	f1 1st Quartile	f1 3rd Quartile
African	36	0.62	0.58	0.65
Americas	30	0.60	0.58	0.63
Eastern Mediterranean	16	0.57	0.50	0.63
European	26	0.49	0.41	0.56
South-East Asia	11	0.64	0.60	0.67
Western Pacific	18	0.51	0.46	0.57

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546 **Table 2.** F1 statistic median (in descending f1 median) by ATC medication category for Model
 547 EML compared to national EML.
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ATC & Medicine Class Name	f1 median	f1 1st Quartile	f1 3rd Quartile	iqr
A01 STOMATOLOGICAL PREPARATIONS	1.00	0.74	1.26	0.52
D09 MEDICATED DRESSINGS	1.00	1.00	1.00	0.00
G01 GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	1.00	0.83	1.17	0.33
A11 VITAMINS	0.80	0.73	0.87	0.15
A12 MINERAL SUPPLEMENTS	0.80	0.68	0.92	0.24
C03 DIURETICS	0.80	0.70	0.90	0.19
A03 DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	0.80	0.64	0.96	0.31
N01 ANESTHETICS	0.77	0.63	0.90	0.27
B03 ANTIANEMIC PREPARATIONS	0.75	0.70	0.80	0.11
C08 CALCIUM CHANNEL BLOCKERS	0.75	0.62	0.88	0.26
H02 CORTICOSTEROIDS FOR SYSTEMIC USE	0.75	0.64	0.86	0.22
N03 ANTIEPILEPTICS	0.73	0.64	0.82	0.18
C07 BETA BLOCKING AGENTS	0.72	0.65	0.79	0.13
J07 VACCINES	0.69	0.56	0.81	0.25
J01 ANTIBACTERIALS FOR SYSTEMIC USE	0.67	0.60	0.74	0.14
C01 CARDIAC THERAPY	0.67	0.56	0.77	0.21
S01 OPHTHALMOLOGICALS	0.67	0.55	0.78	0.22
B01 ANTITHROMBOTIC AGENTS	0.67	0.55	0.78	0.22
L04 IMMUNOSUPPRESSANTS	0.67	0.52	0.82	0.30
C02 ANTIHYPERTENSIVES	0.67	0.49	0.84	0.36
H03 THYROID THERAPY	0.67	0.52	0.81	0.29
C05 VASOPROTECTIVES	0.67	0.47	0.87	0.40
D07 CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	0.67	0.37	0.97	0.60
H01 PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES	0.67	0.56	0.78	0.22
M04 ANTIGOUT PREPARATIONS	0.67	0.50	0.83	0.33
P03 ECTOPARASITICIDES, INCL. SCABICIDES, INSECTICIDES AND REPELLENTS	0.67	0.41	0.92	0.51
N05 PSYCHOLEPTICS	0.63	0.52	0.74	0.22
J04 ANTIMYCOBACTERIALS	0.62	0.54	0.71	0.17
L01 ANTINEOPLASTIC AGENTS	0.62	0.43	0.80	0.38
A02 DRUGS FOR ACID RELATED DISORDERS	0.60	0.45	0.75	0.31

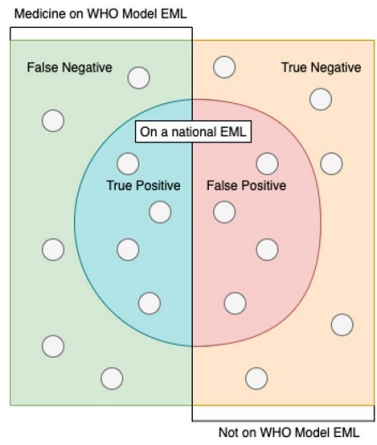
A07 ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	0.60	0.49	0.71	0.21
A10 DRUGS USED IN DIABETES	0.60	0.52	0.68	0.17
D01 ANTIFUNGALS FOR DERMATOLOGICAL USE	0.60	0.52	0.68	0.17
D06 ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	0.60	0.47	0.72	0.25
J06 IMMUNE SERA AND IMMUNOGLOBULINS	0.60	0.47	0.73	0.27
N02 ANALGESICS	0.59	0.48	0.69	0.21
A06 DRUGS FOR CONSTIPATION	0.57	0.49	0.65	0.17
R03 DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	0.57	0.49	0.65	0.17
J02 ANTIMYCOTICS FOR SYSTEMIC USE	0.57	0.48	0.66	0.18
N04 ANTI-PARKINSON DRUGS	0.57	0.41	0.73	0.31
R05 COUGH AND COLD PREPARATIONS	0.57	0.40	0.75	0.35
B02 ANTIHEMORRHAGICS	0.54	0.38	0.70	0.33
G03 SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	0.52	0.44	0.61	0.17
N06 PSYCHOANALEPTICS	0.50	0.36	0.64	0.28
P02 ANTHELMINTICS	0.50	0.32	0.68	0.35
M03 MUSCLE RELAXANTS	0.50	0.33	0.67	0.33
N07 OTHER NERVOUS SYSTEM DRUGS	0.50	0.37	0.63	0.27
A04 ANTIEMETICS AND ANTINAUSEANTS	0.50	0.17	0.83	0.67
D10 ANTI-ACNE PREPARATIONS	0.50	0.17	0.83	0.67
G02 OTHER GYNECOLOGICALS	0.50	0.10	0.90	0.80
J05 ANTIVIRALS FOR SYSTEMIC USE	0.49	0.40	0.57	0.17
V03 ALL OTHER THERAPEUTIC PRODUCTS	0.44	0.31	0.58	0.27
C09 AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	0.44	0.23	0.66	0.43
M01 ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	0.44	0.31	0.58	0.26
P01 ANTIPROTOZOALS	0.41	0.27	0.56	0.29
L02 ENDOCRINE THERAPY	0.40	0.33	0.47	0.15
L03 IMMUNOSTIMULANTS	0.40	0.31	0.49	0.17
R01 NASAL PREPARATIONS	0.40	0.10	0.70	0.60
C10 LIPID MODIFYING AGENTS	0.22	0.00	0.56	0.67
R06 ANTIHISTAMINES FOR SYSTEMIC USE	0.17	0.03	0.32	0.29
A09 DIGESTIVES, INCL. ENZYMES	0.00	0.00	0.25	0.50
B05 BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	0.00	0.00	0.25	0.50
D02 EMOLLIENTS AND PROTECTIVES	0.00	0.00	0.25	0.50

D04 ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	0.00	0.00	0.50	1.00
D05 ANTIPSORIATICS	0.00	0.00	0.33	0.67
D08 ANTISEPTICS AND DISINFECTANTS	0.00	0.00	0.00	0.00
D11 OTHER DERMATOLOGICAL PREPARATIONS	0.00	0.00	0.50	1.00
H04 PANCREATIC HORMONES	0.00	0.00	0.50	1.00
M05 DRUGS FOR TREATMENT OF BONE DISEASES	0.00	0.00	0.13	0.26

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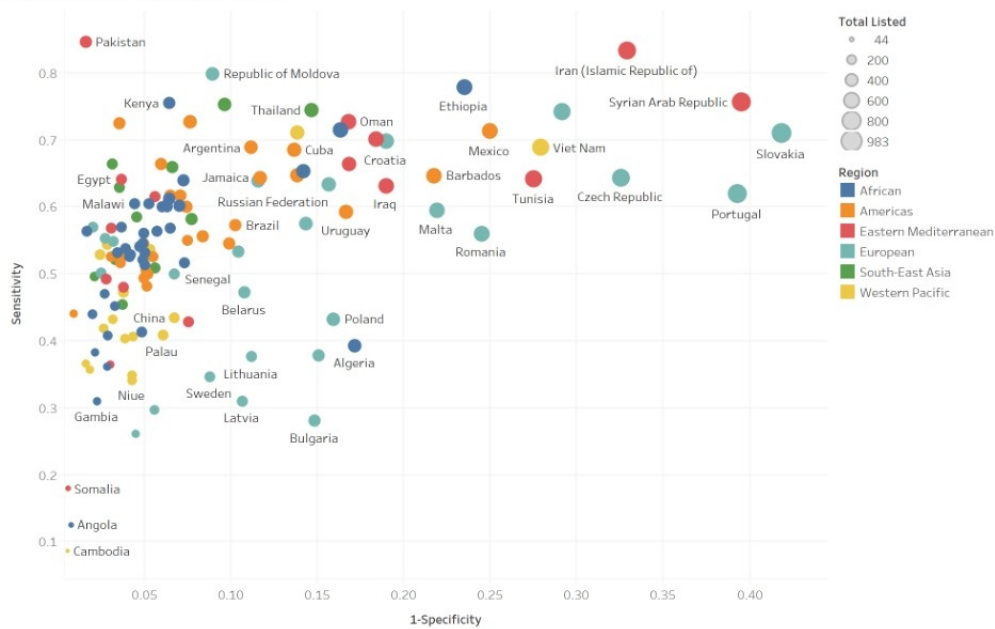


Precision = $\frac{\text{True Positive}}{\text{True Positive} + \text{False Positive}}$

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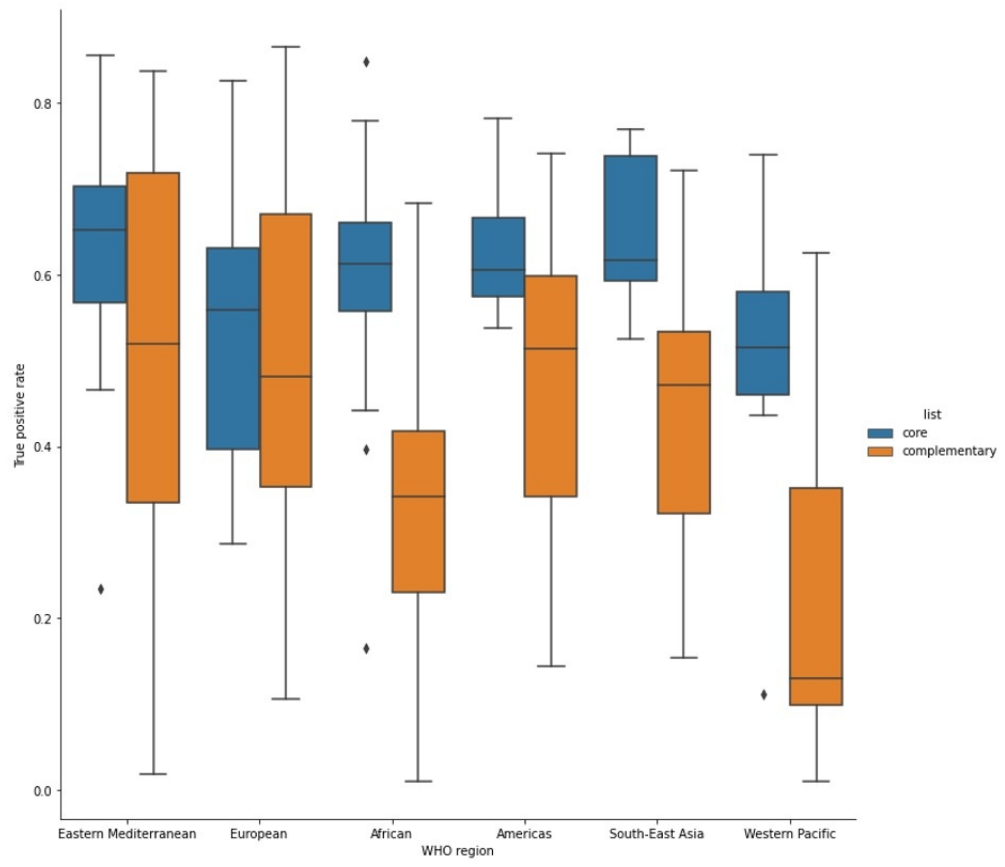
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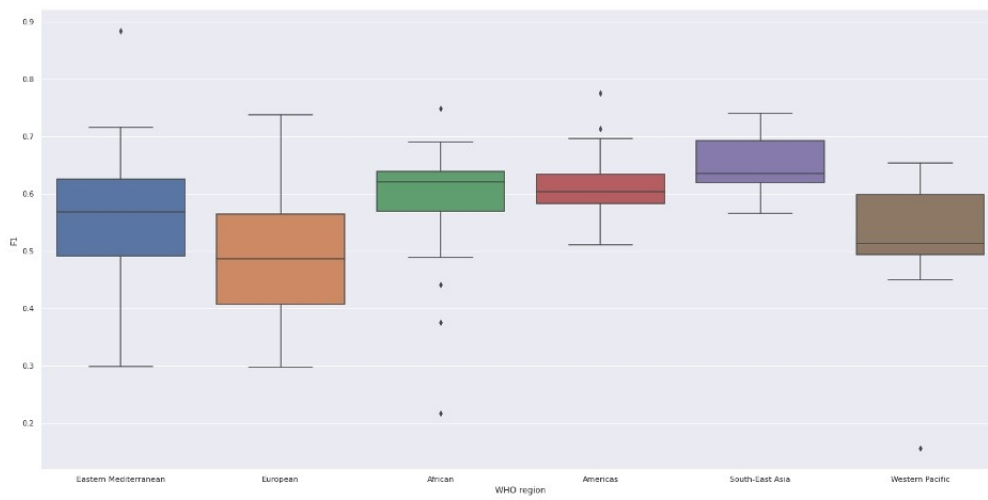
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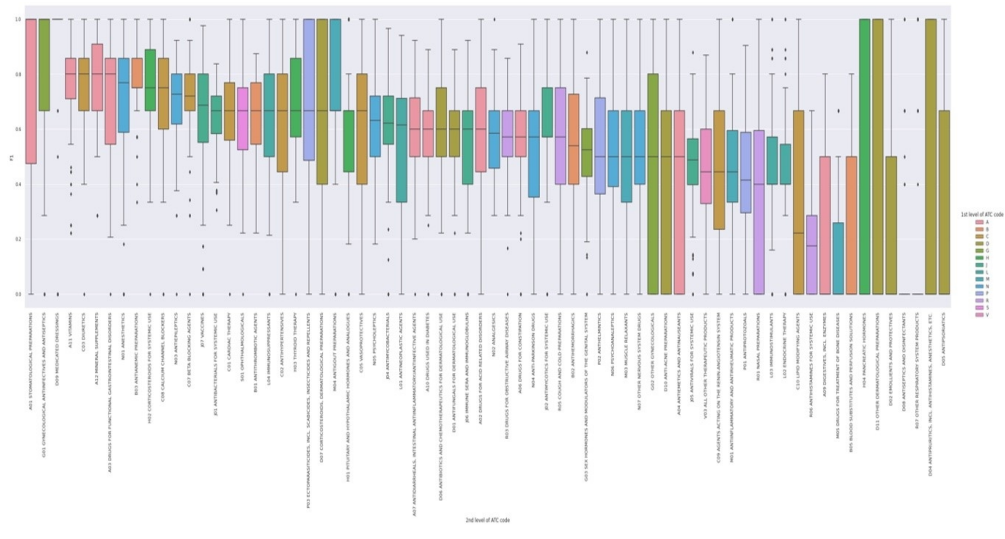
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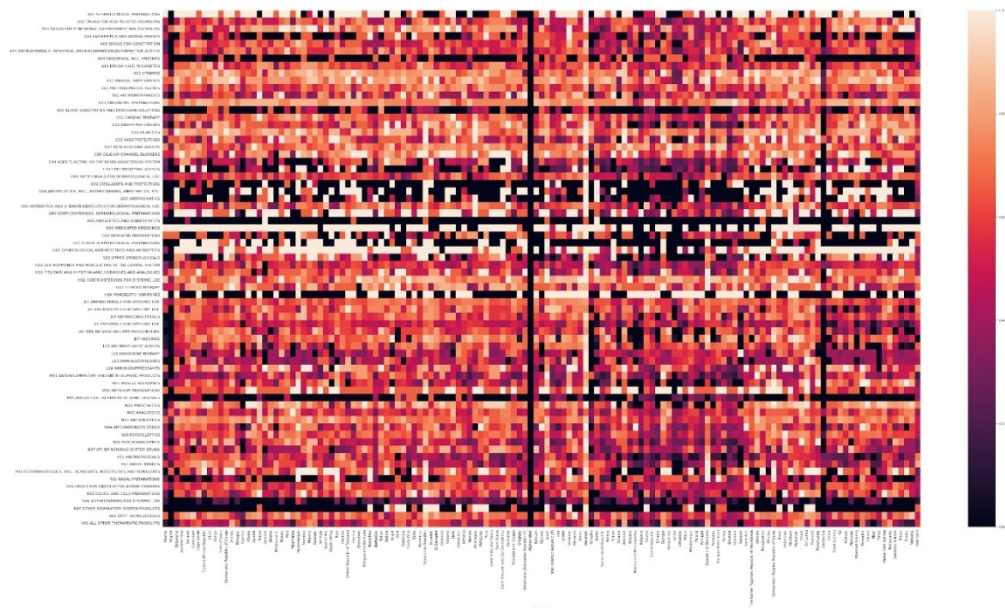
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