Importance of high quality data -
Supporting dose capture

Alem Zekarias, Pharmacovigilance Scientist
Annual meeting for International Medication Safety Network
November 14

2022-11-14

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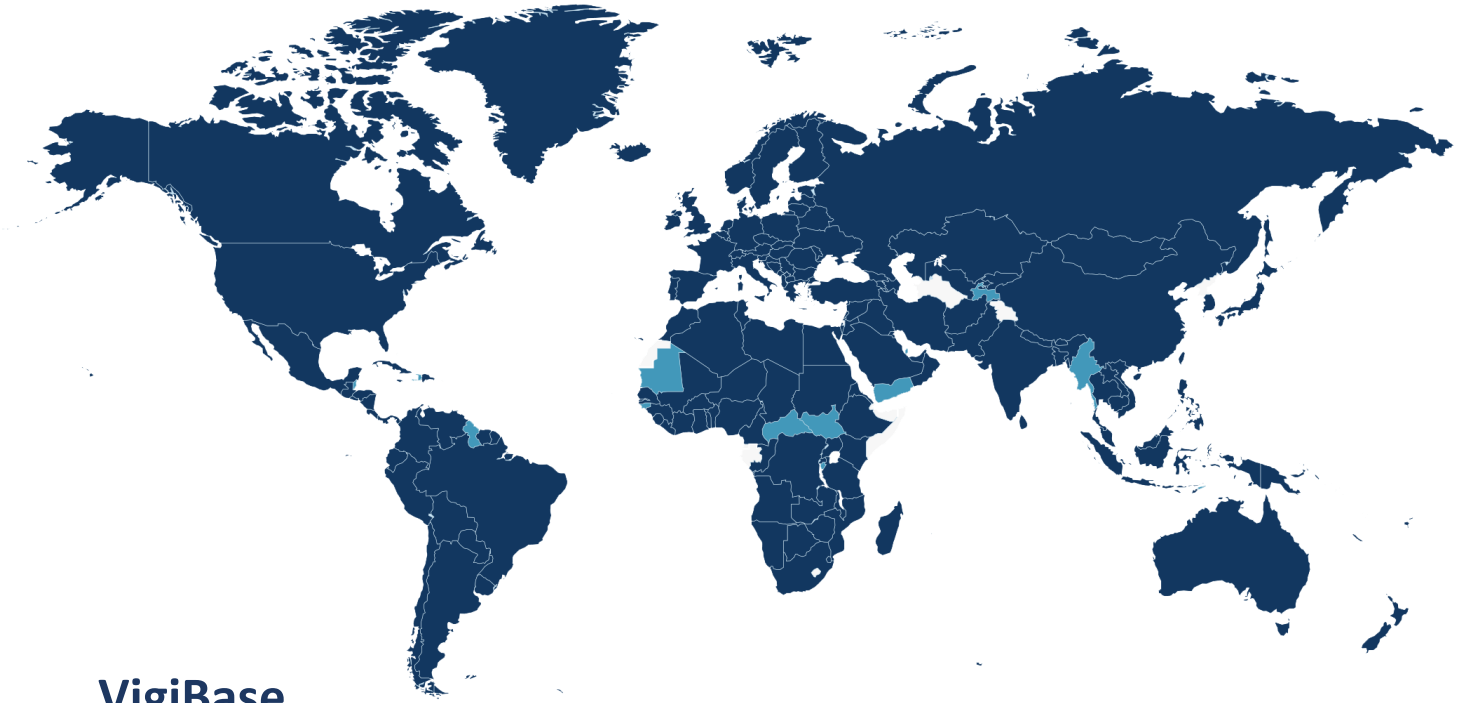
WHO Programme for International Drug Monitoring

Programme coverage

- 153 full members
- 22 associate members
- Non-member

Covers > 99% of World population



Programme member benefits

PIDM members have access to UMC's resources and expertise, including tools, training, support, knowledge sharing.

VigiBase

Most records in VigiBase are submitted by the national pharmacovigilance centres (NCs) in member countries

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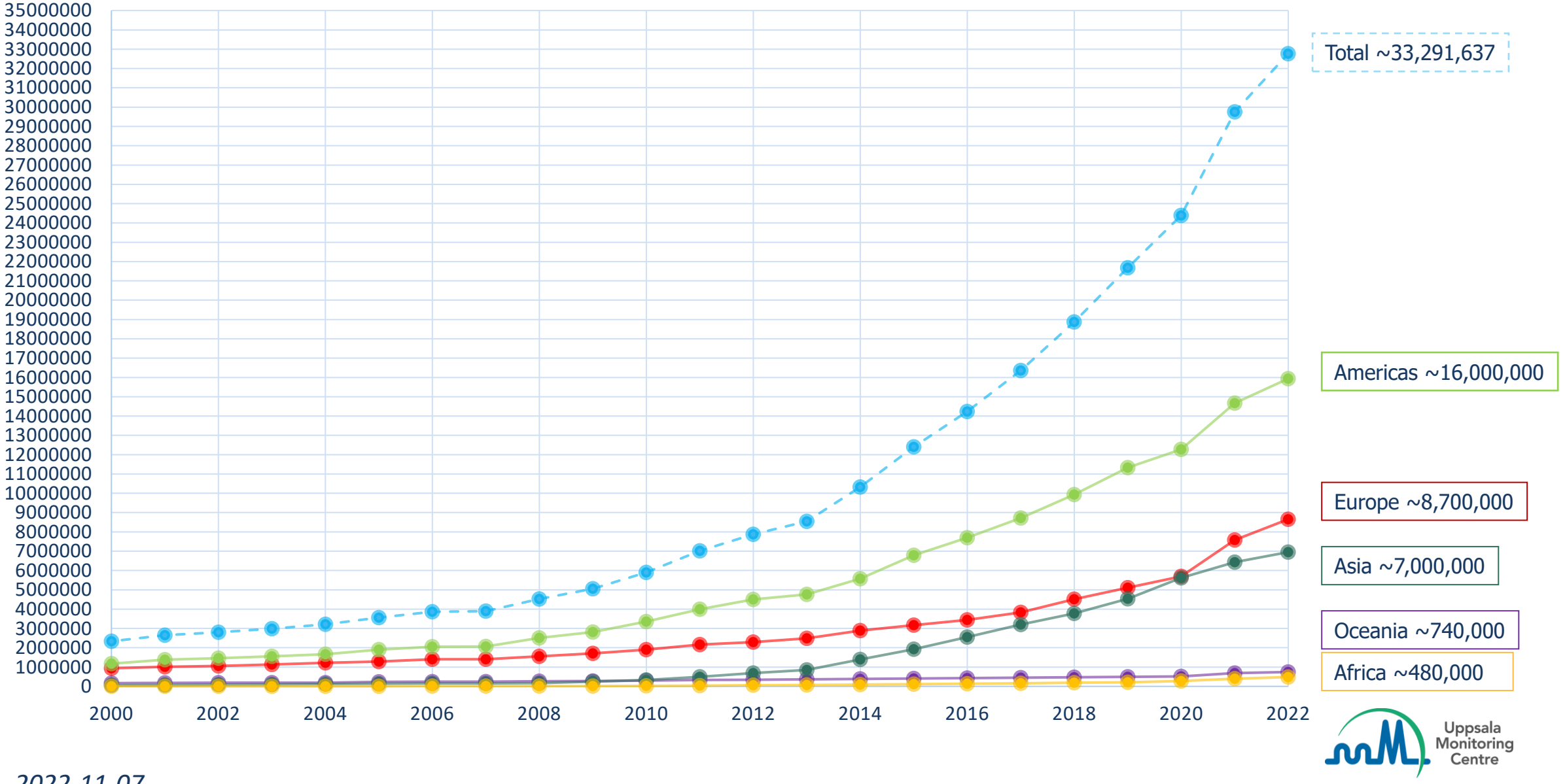
Cumulative count of ICSRs (per continent)



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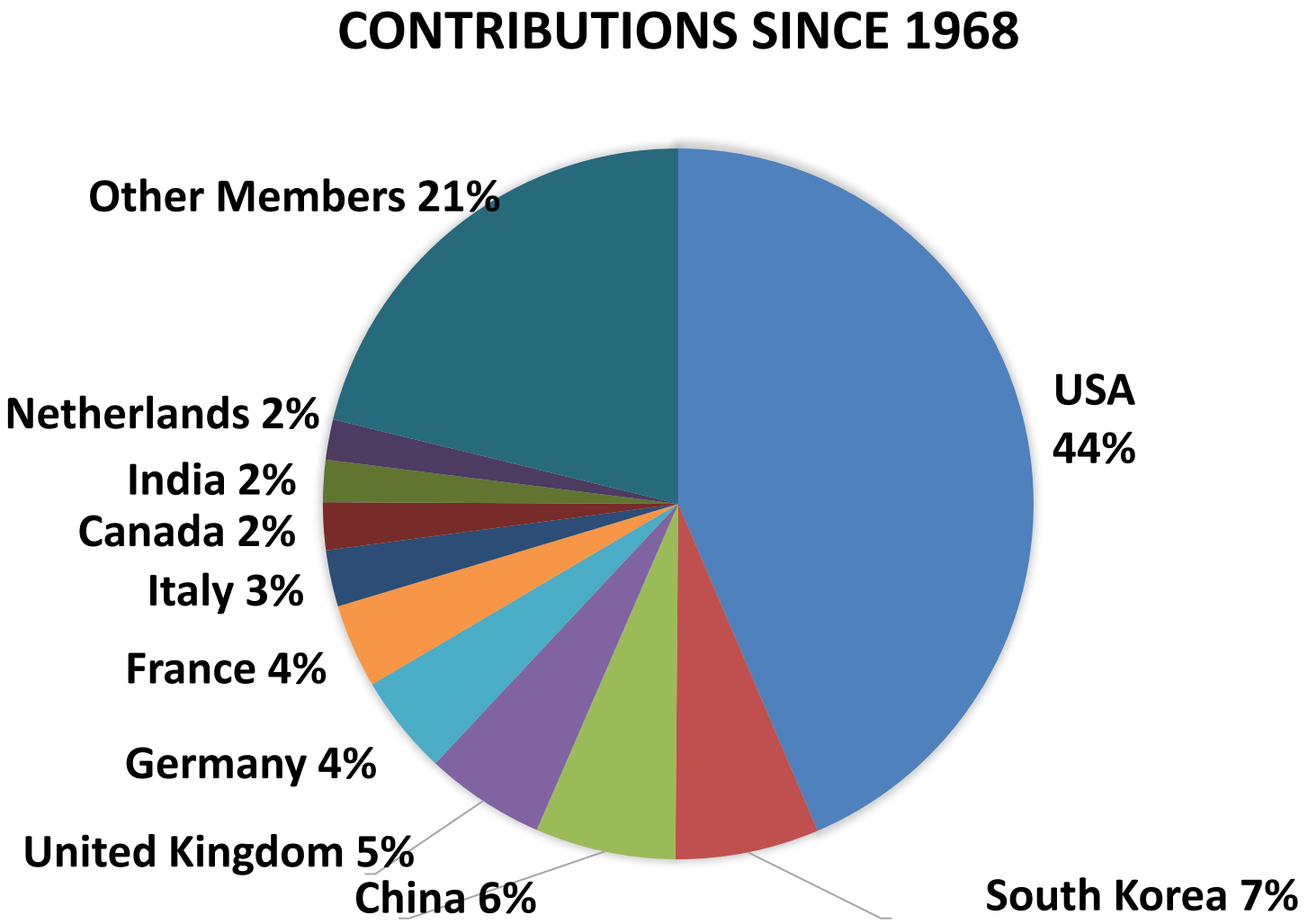
VigiBase Basics

- Major contributors like USA and EU+UK have been members for a long time.
- Asia increases rapidly with large yearly contributions from e.g. South Korea and China.



2022-10-04

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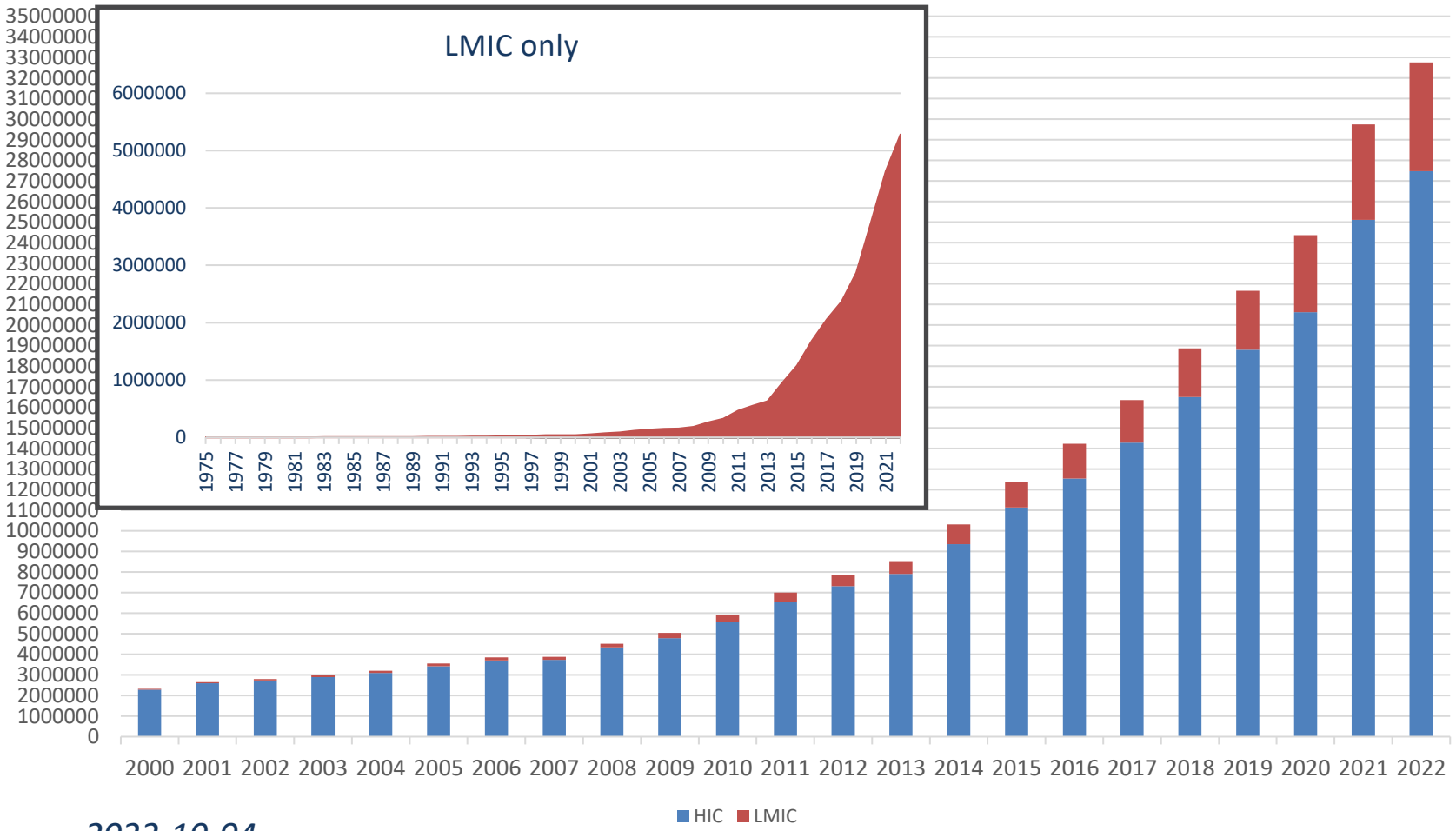
HIC's and LMIC's contribution - cumulative



16% from LMICs

LMICs:
Low and Middle Income Countries

HICs:
High Income Countries

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Medication error coded reports in VigiBase – statistics

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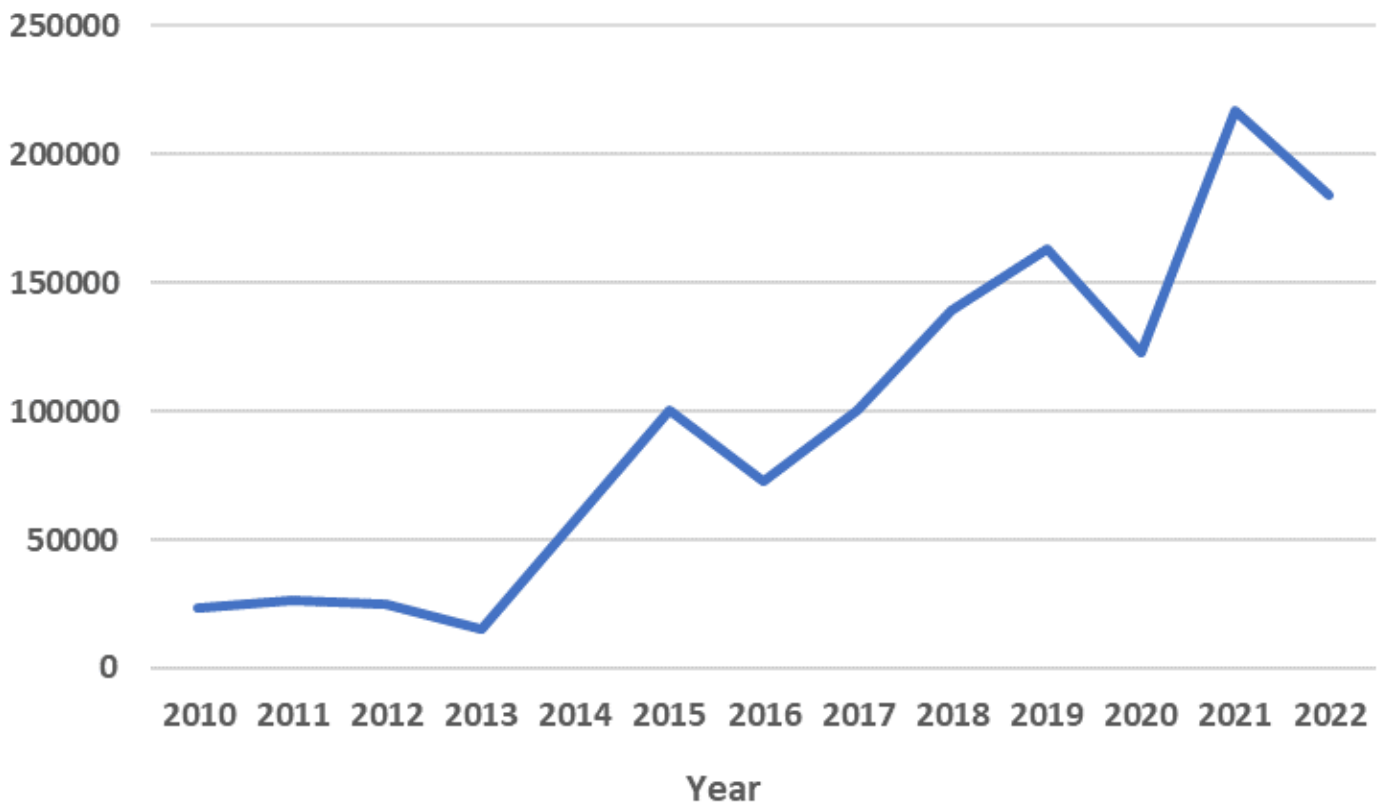
Number of Medication error coded reports in VigiBase



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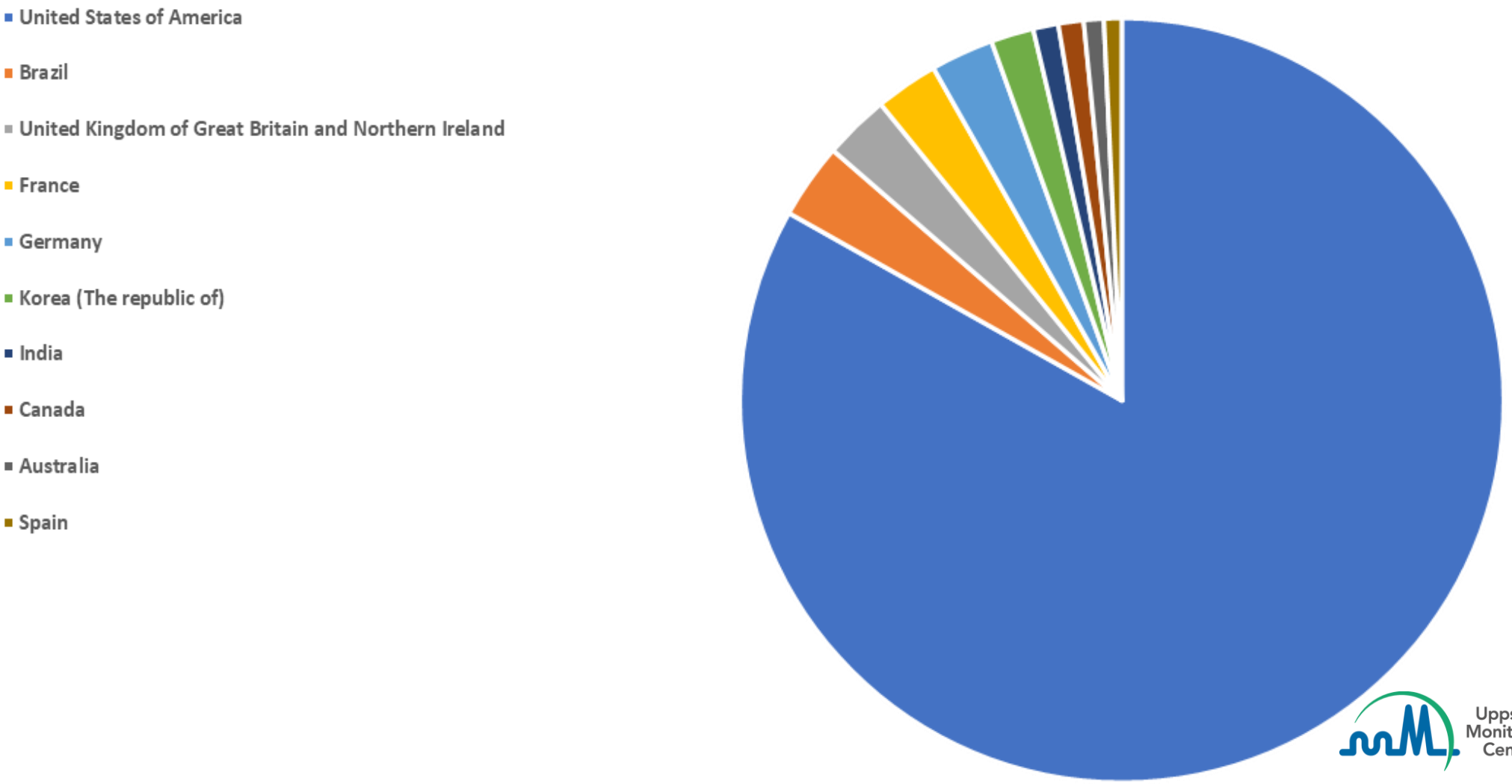
Top reporting countries



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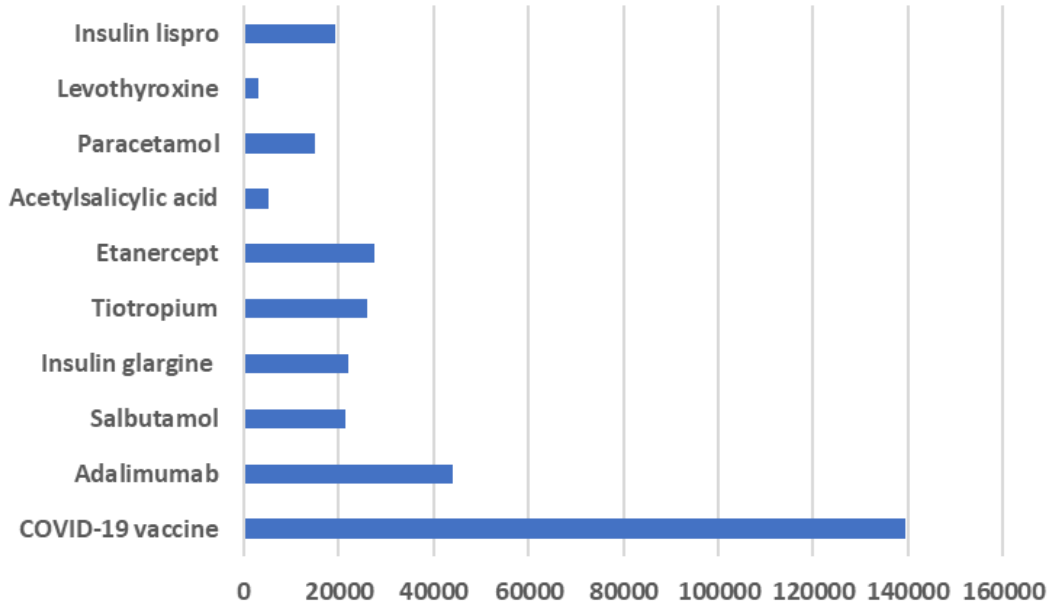
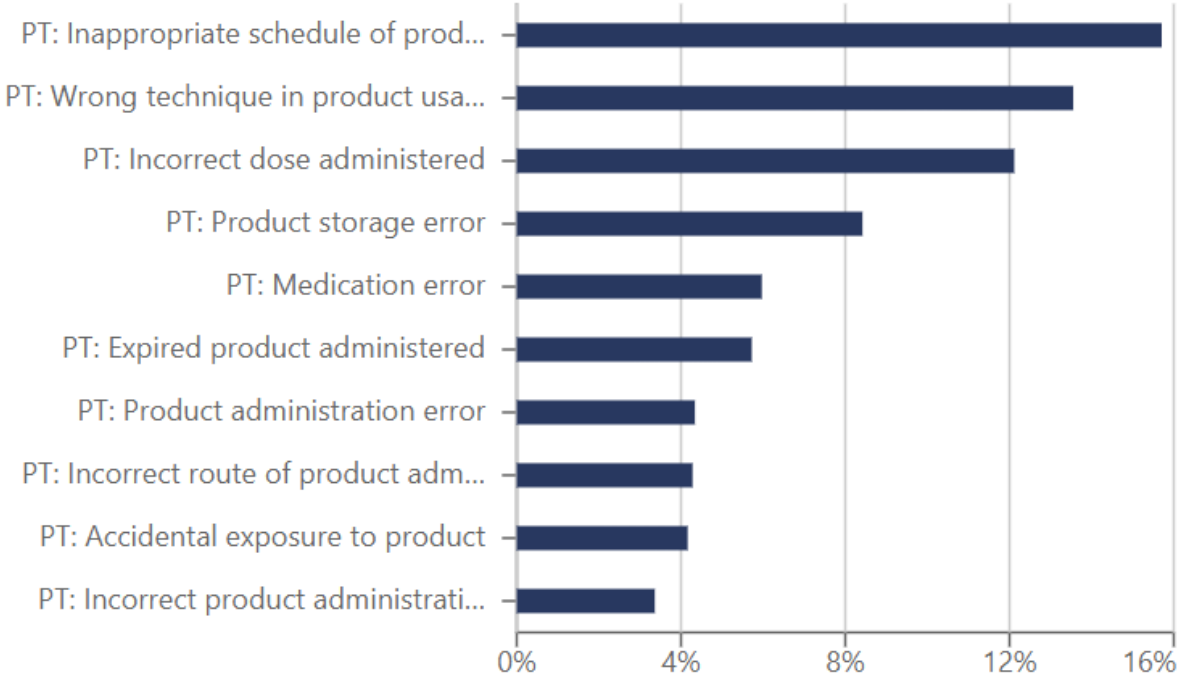
Most reported drugs/vaccines and terms in VigiBase





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Supporting capture of correct and complete dose information in VigiBase

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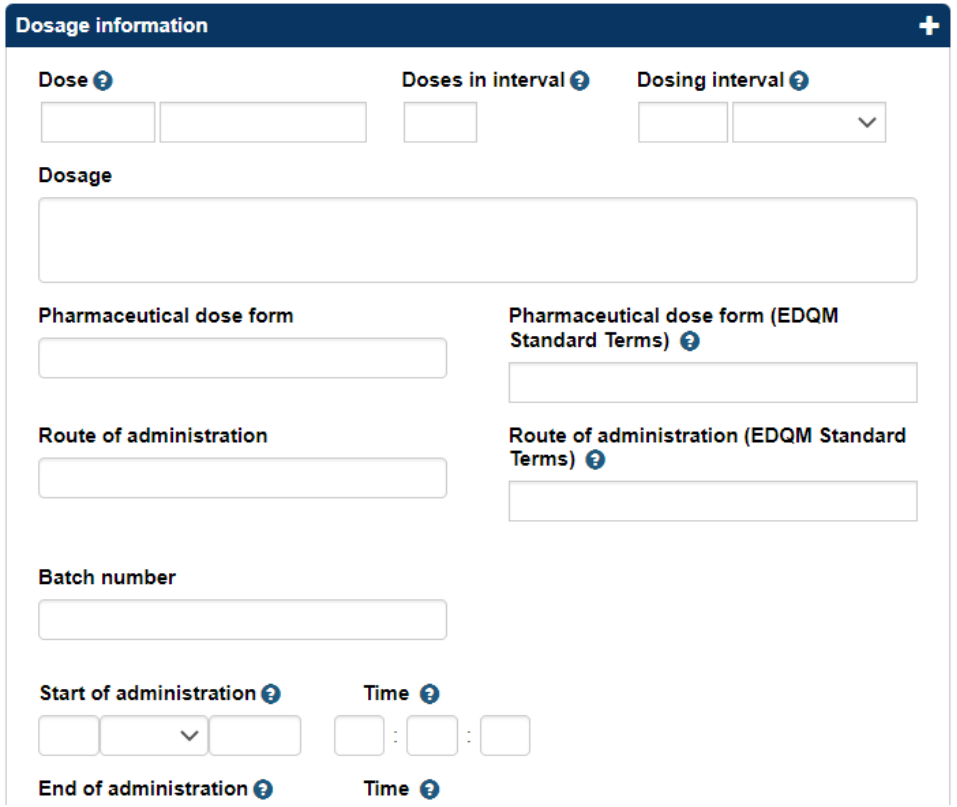
Previous research

- Lack of dose information
- Incorrect entered dose information
- Too high dose – no reflection

- Can we better support the reporter?
  - Enter dose
  - Complete and correct
  - Reflect on potential signals beyond causality assessment



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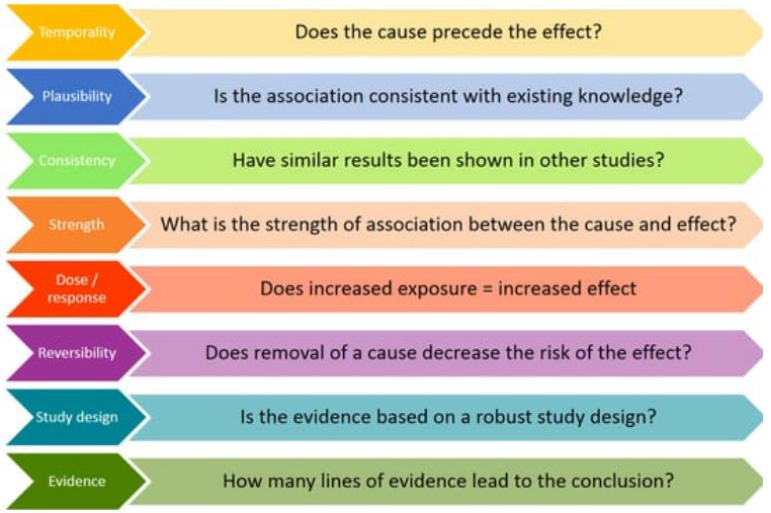
Dose central to causality and preventability assessment 1(2)

- Causality assessment
  - Bradford Hill – **Biological gradient/Dose-response relationship**
  - The **Naranjo Algorithm**, or Adverse Drug Reaction Probability Scale



- Preventability method
  - **Preventability assessment**

Table 1 Preventability criteria in the P Method (PM)

Factors related to:	Preventability criteria
Healthcare professionals' practices ('Pr')	1. Incorrect dose?
	2. Incorrect drug administration route?
	3. Incorrect drug administration duration?
	4. Incorrect drug dosage formulation administered?
	5. Expired drug administered?
	6. Incorrect storage of drug?
	7. Drug administration error (timing, rate, frequency, technique, preparation, manipulation, mixing)?
	8. Wrong indication?
	9. Inappropriate prescription according to the characteristics of the patient (age

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Dose central to causality and preventability assessment 2(2)

- Interactions: CYP-inhibitors/stimulators
  - **Increased** effect, **decreased** effect and/or Adverse drug reactions (**ADRs**)
- Dose adjustments
  - Dose **titration**
  - **Reduction** due to hepatic/kidney impairment

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The importance of dose information

- Assess reports including **dose related terms**
  - 30 terms mentioning ”dose” as preferred term (PT)
  - **862 993 reports**
- **Weight based drugs** difficult to confirm reported dose
  - Antibiotics
  - Biological
  - Etc…

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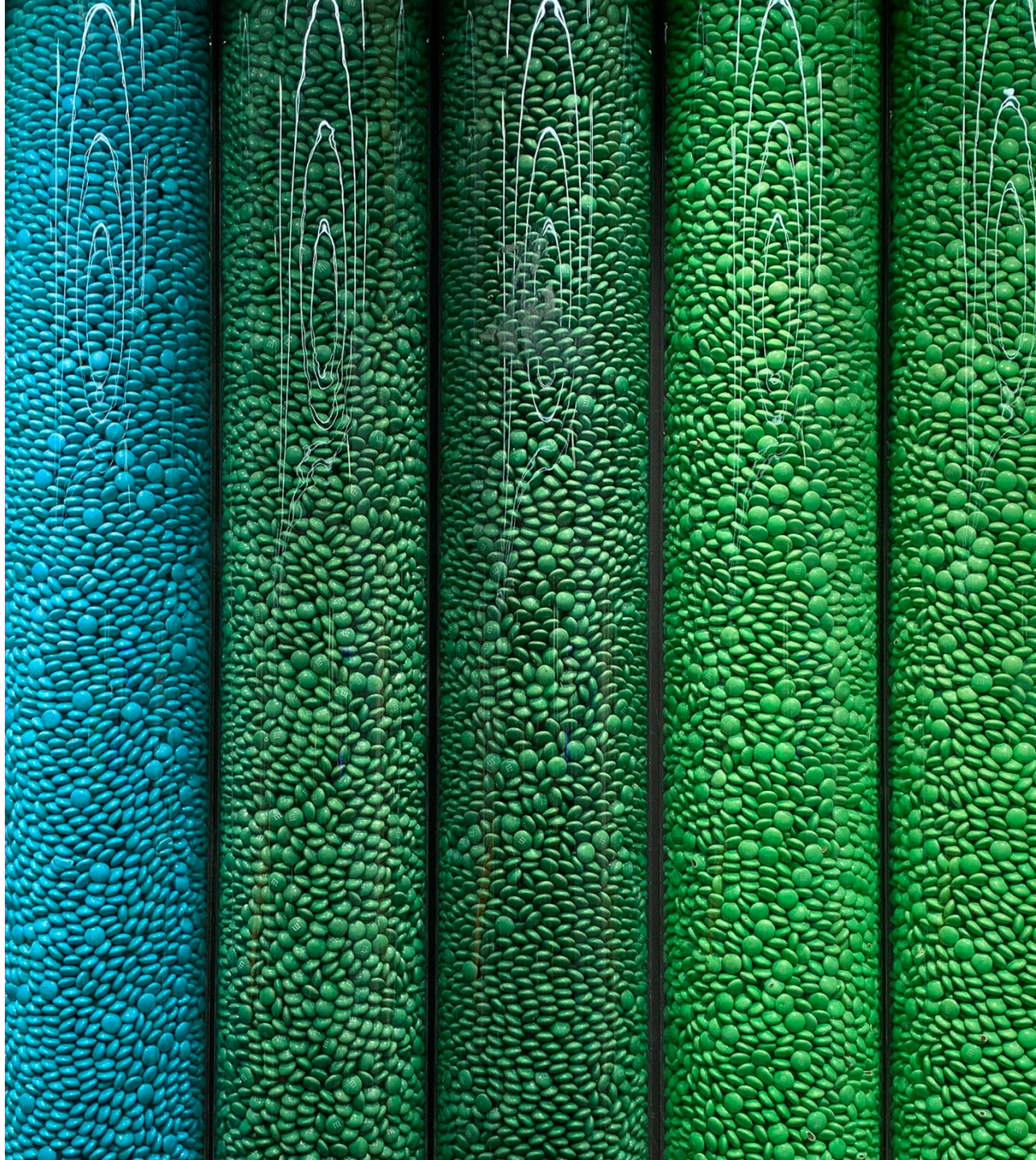
Why structured dose information?

- Can compute daily dose automatically
- For large case series
- When narrative and free-text information is not shared
- Easy and time efficient to find the dose information on the report



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Dose statistics

	VigiBase	VigiFlow
Total number drug enteries **<u>Excluding</u>** ***- Foreign reports*** ***- Duplicates*** ***- Concomitant*** ***- Vaccines***	39,413,117	1,409,203
With all structured dose fields filled	9,648,280	208,543
Proportion	24,5%	15,2%

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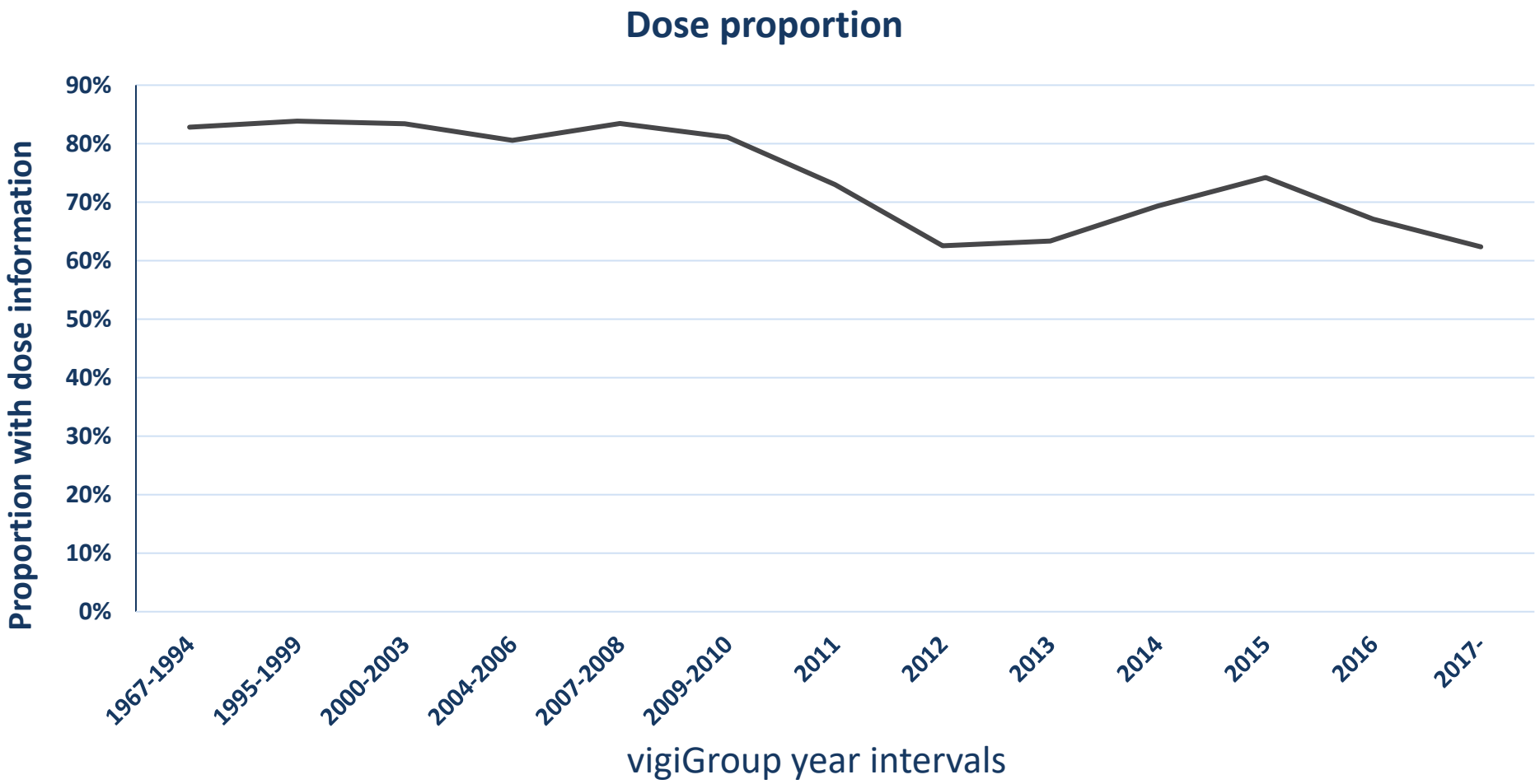
vigiPoint



Excluding vaccines, duplicates and foreign reports

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2022-03-31

Dose information quality

- Examples of erroneously coded doses

Drugs

WHODrug active ingredient variant *WHODrug trade name* *Reported medication*	Role	Start date End date	Treatment duration	Dosage regimen	Route of admin.	Indication	Action taken with drug
Nevirapine *Nevirapine* *Nevirapine*	Suspect	16 Mar 2009 –	1 month	200 mg, 12 per 12 hours	Oral	Acute hiv infection syndrome	Dose not changed

Drugs

WHODrug active ingredient variant *WHODrug trade name* *Reported medication*	Role	Start date End date	Treatment duration	Dosage regimen	Route of admin.
Amodiaquine hydrochloride *Amodiaquine hydrochloride* *Amodiaquine hydrochloride*					
Dosage text: 300 mg *Dosage form: comprimé* *Cumulative dose: 900 mg*					
Artesunate *Artesunate* *Artesunate*	Concomitant	28 Jan 2009 30 Jan 2009	3 days	150 mg, 150 per – days	Oral
Dosage form: comprimé *Cumulative dose: 150 mg*					

Ethambutol;Isoniazid *Ethambutol;Isoniazid* *Ethambutol w/isoniazid*	Concomitant	18 Dec 2005 18 May 2006	5 months	1100 mg, 1 per 1 day	Oral
Additional information: the patient was taking 800mg ethambutol and 300mg isoniazid *Dosage form: TABLET*					

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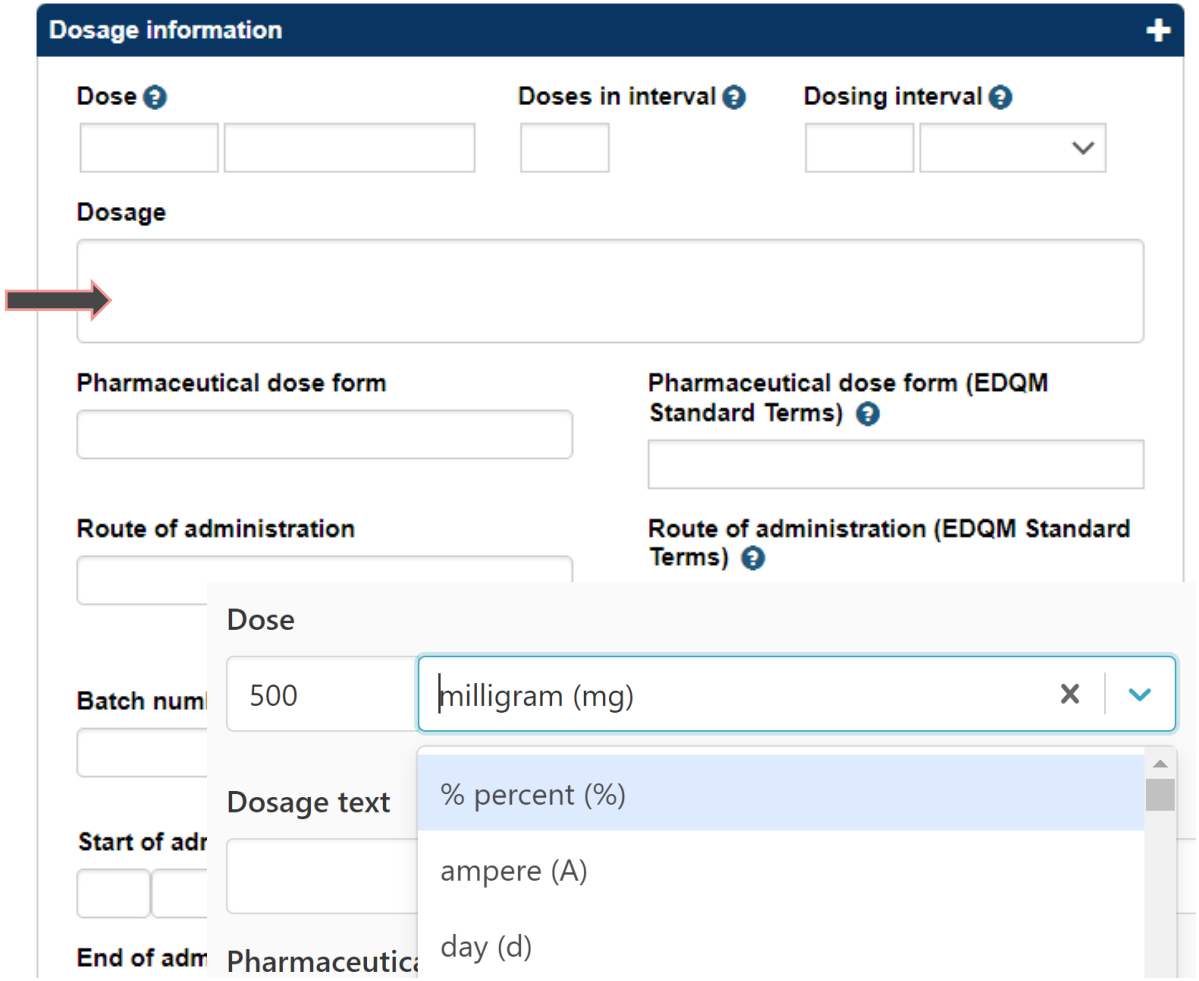
How can VigiFlow countries report dose?

- Number of fields – overwhelming
- Challenging to understand where to fill in what information
- Free text filed used instead (12 million reports)
- Non-supportive interface
  - Not data-driven suggestions/support
  - Many choices
  - No sanity checks



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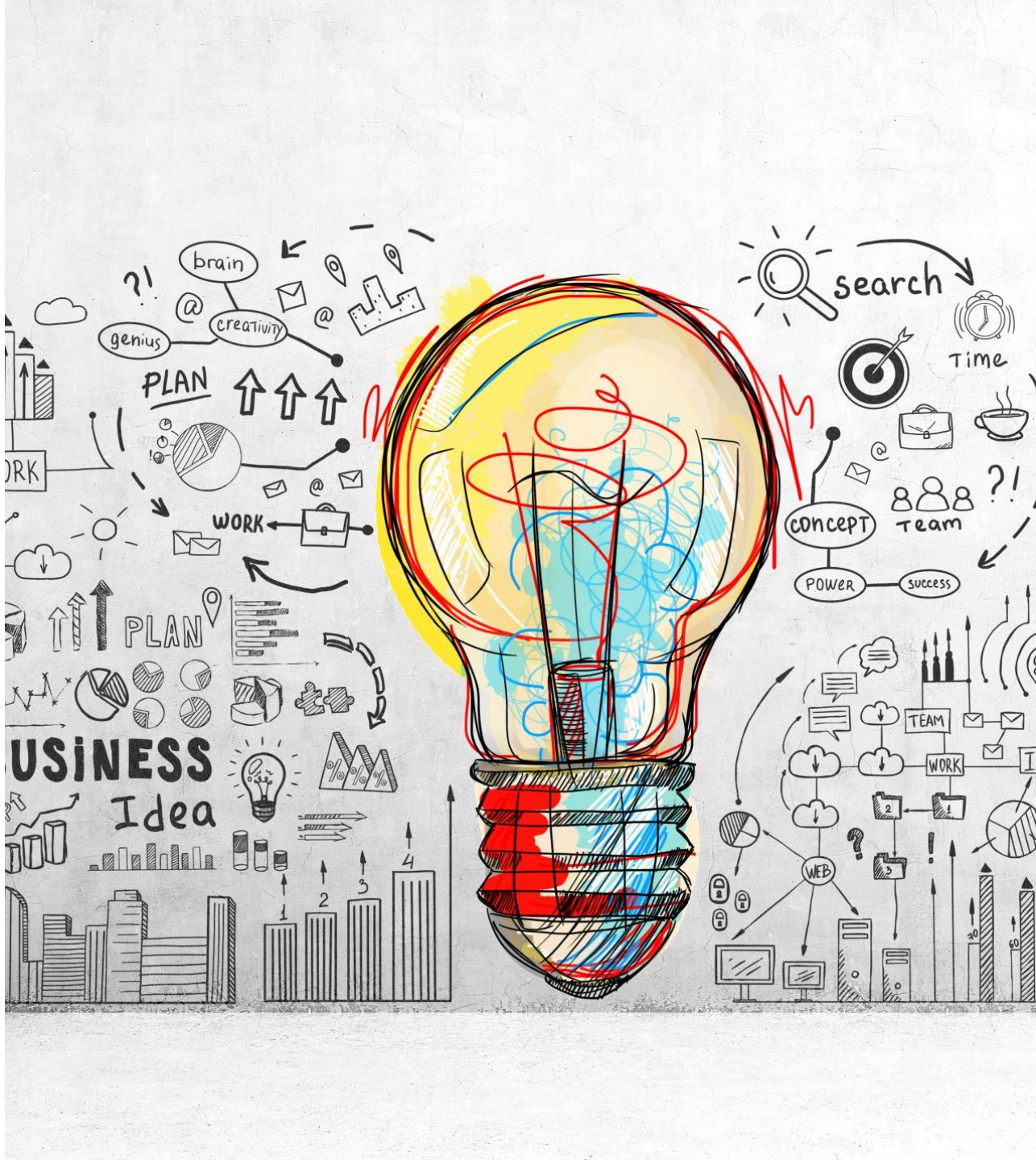
Improvement ideas

- Data-driven suggestions
- A simple entry and an advanced one
- Sanity checks and alerts
- Help to reflect on signals **beyond** causality



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Effect goals

1. To **increase** the proportion of reports in VigiBase including dose information.
2. The entered dose be as **precise** and **complete** as possible (quality).

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Standard units, dose-interval and frequency

Mg milligram(s)	657788
DF dosage form	76496
G gram(s)	51641
µg microgram(s)	34380
Iu international unit(s)	27931
ml millilitre(s)	27285
mg/kg milligram(s)/kilogram	6930
Gtt drop(s)	5983
mg/m 2 milligram(s)/sq. meter	5313
MCi millicurie(s)	4327
% percent	1856
Miu iu(1,000,000s)	1626

Day	461510
Week	78236
Hour	72646
Total	59146
Month	25838
Cyclical	14719
AsNecessary	3554
Year	3313
Minute	1054

nan times per nan None	2555257
1.0 times per 1.0 Day	377565
nan times per 1.0 Day	363014
2.0 times per 1.0 Day	112223
nan times per nan Total	86397
1.0 times per 1.0 Week	39901
3.0 times per 1.0 Day	36713
nan times per 0.5 Day	35308
1.0 times per nan None	34423
nan times per 24.0 Hour	29635
nan times per 1.0 Week	29237
nan times per 21.0 Day	29018
1.0 times per 12.0 Hour	26878
nan times per 12.0 Hour	23521
1.0 times per 1.0 Month	22943
nan times per 1.0 Month	19914
nan times per nan Cyclical	18606
1.0 times per 2.0 Week	17552
nan times per 8.0 Hour	17357

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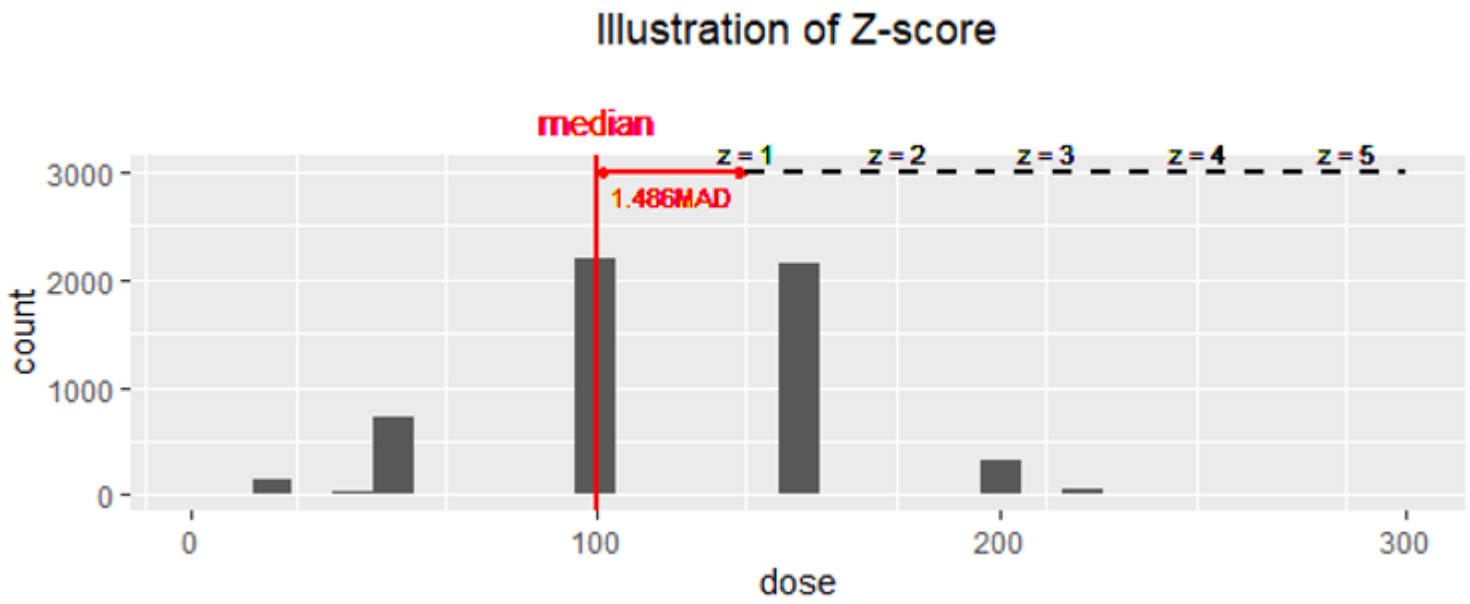
Threshold identification – high dose

The modified z-score was calculated for the set of reported doses X as

$$\text{mod. z-score} = \frac{x_i - median(X)}{1.486 * \text{MAD(X)}}$$



Prototype – dose entering 1(2)

Drug

Paracetamol

There are 71742 reports in total with complete dose information in VigiBase for Paracetamol.

Most commonly reported dosage unit in VigiBase: Mg milligram(s)

Standard Advanced

Value	Unit	Frequency
500	Mg milligram(s)	three times a day

This corresponds to a total daily dose of: 1500.0 Mg milligram(s) per day.

Median dose in VigiBase: 1500.0 Mg milligram(s)

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Prototype – dose entering 2(2)

Drug

Paracetamol

There are 71742 reports in total with complete dose information in VigiBase for Paracetamol.

Most commonly reported dosage unit in VigiBase: Mg milligram(s)

Standard Advanced

Value	Unit	Value			Per day/hour/week/...?
5000	Mg milligram(s)	3	times	every 1	day(s)

This corresponds to a total daily dose of: 15000.0 Mg milligram(s) per day.

This is a high daily dose as compared to commonly reported doses in VigiBase (in mg).

Median dose in VigiBase: 1500.0 Mg milligram(s)

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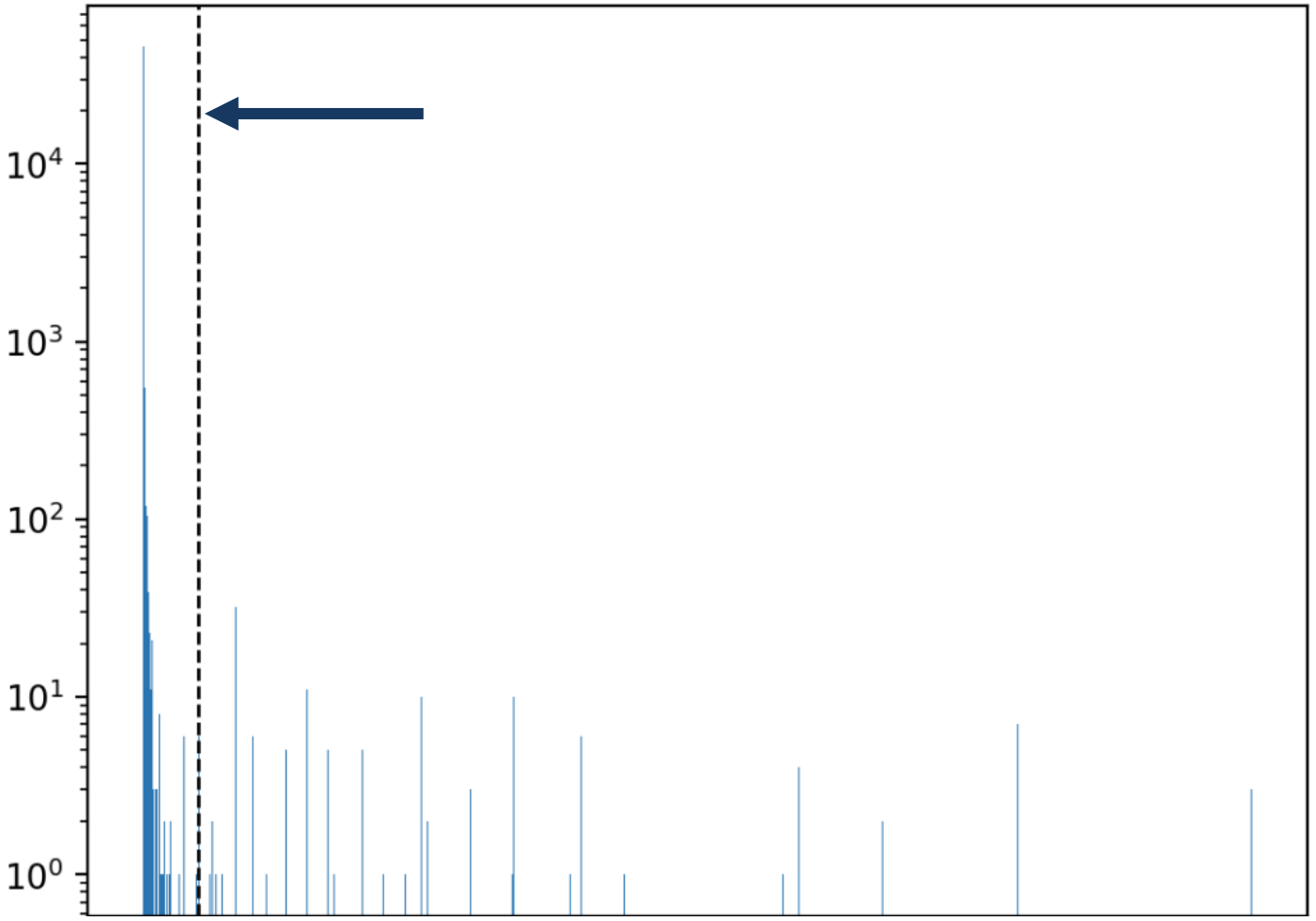
Outlying dose distribution



- Demonstrate the entered dose compared to all paracetamol-related reports shared in VigiBase.
- Considering indication, age, route of administration for reference distribution

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Future improvements

- Include additional dosages
- Initiate the work around reflecting on possible preventable drug errors
- Evaluate its usefulness and impact

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Advancing medicines **safety together**

alem.zekarias@who-umc.org

Uppsala Monitoring Centre (UMC)
Box 1051, SE-751 40 Uppsala, Sweden
Email: info@who-umc.org, www.who-umc.org

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