

# Improving National Drug List Harmonization Through an Eight-Pattern Analysis of WHO ATC/DDD Classifications

Mohammad Javad Rajabi

rajabi.pharma@gmail.com

Shahid Beheshti University of Medical Sciences

Mitra Mahmoudi-Meymand

Kerman University of Medical Sciences

Mehrdad Vesali-Sharif

Shahid Beheshti University of Medical Sciences

---

## Article

**Keywords:** ATC/DDD system, Multiclassification, National Drug List, Drug Utilization

**Posted Date:** July 2nd, 2026

**DOI:** <https://doi.org/10.21203/rs.3.rs-9907658/v1>

**License:** © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

**Additional Declarations:** No competing interests reported.

---

## Abstract

## Background

The Anatomical Therapeutic Chemical (ATC) classification and Defined Daily Dose (DDD) system of the World Health Organization are recognized internationally as the platinum standard in research methodology related to drug use. Our focus is on drugs with multiple ATC codes and those with discrepancies in Administration Routes (Adm.R) and DDIs. A list of these medications was created to alert drug agencies about the critical need for auditing and verifying the accuracy of their national list harmonizations.

## Methods

An 8-Pattern Classification Framework has been accordingly developed from the World Health Organization (WHO) primary data by combining ATC code, DDD values, and Adm.R, in order to classify 913 pair drugs that belong to multiple classifications.

## Results

our analysis shed light that between 2714 medication in WHO/DDD classification that have DDD, 913 pairs have satisfied one of the 8-conditions. that 1 molecule in condition 1 that have similar ATC, DDD and Adm.R to 402 medications in class 2 that have similar ATC, similar DDD and different Adm.R.

## Conclusion

It is very important to correctly classify multi-classified drugs towards just drug procurement and use reporting. We introduce the 8-Pattern Approach to make national list discrepancies conform to the global classifications defined for proper reporting of drug use.

## Introduction

Monitoring drug consumption requires a robust classification scheme and a standardized unit of measurement. In the early 1980s, the World Health Organization (WHO) established the Anatomical Therapeutic Chemical (ATC) classification system as the gold standard for drug utilization research. Utilized for decades by numerous countries and international institutions, the ATC/DDD system serves to describe and compare drug consumption patterns, support pharmacovigilance, and facilitate cross-national statistical comparisons. Accurate ATC classification and correct Defined Daily Dose (DDD) assignment are vital for national drug regulatory agencies to effectively plan procurement, ensure medicine availability, and monitor utilization patterns. To maintain the comparability of longitudinal trends and ensure the stability of the framework, these codes and doses have remained largely unrevised over time. The DDD provides a technical and comparative unit that overcomes many limitations of traditional volume-based metrics, offering a fixed unit of measurement independent of price, currencies, or package size[1].

The ATC system features a rigorous five-level structure, classifying medicines based on three primary indicators: the ATC code, the DDD, and the route of administration (Adm.R). A primary challenge in harmonizing national drug lists is the assignment of multiple codes to a single active substance. This complexity primarily arises from two structural patterns: differentiation by route of administration (e.g., the diverse codes assigned to prednisolone) and, less commonly, medicinal strength (e.g., the classification of finasteride in either dermatological or urological groups). Furthermore, in cases of multiple indications despite fixed doses and strengths, the WHO adopts a single-code determination approach based on global predominant use. While this approach ensures macro-statistical stability, it can lead to significant classification conflicts in national drug systems where clinical utilization patterns do not align with global assumptions[1].

Despite its global standing, the ATC system faces contemporary challenges due to its single-indication logic, particularly in classifying pleiotropic drugs such as Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors or gabapentinoids[2]. The WHO's policy of assigning a single code based on predominant use often fails to align with national clinical patterns or medicines characterized by multiple indications, administration routes, or varying strengths[1]. This structural misalignment and the resulting phenomenon of multiclassified medicines compromise statistical integrity, hinder cross-national comparisons, and complicate reimbursement policies, often leading to arbitrary decision-making in the development of National Drug Lists (NDLs)[2]. To address these discrepancies and minimize potential calculation errors in drug utilization research, the present study introduces a novel 8-Pattern Classification Framework for the standardized identification of these medicines. This framework aims to provide a comprehensive, evidence-based reference for national regulatory authorities to achieve rigorous and transparent harmonization of their drug lists.

## Method

To address the inherent heterogeneity of the ATC/DDD system, where a single pharmaceutical entity may be associated with multiple ATC codes or varying DDDs, a standardized harmonization approach was essential. We developed a novel 8-Pattern Classification Framework to systematically resolve these structural discrepancies. This framework was based on the combinatorial permutations of three key parameters: ATC code, DDD value, and Adm.R.

Using WHO source data, we constructed a decision tree to categorize all potential scenarios. Since each of the three parameters could either be uniform or divergent across records, a total of eight distinct situations  $2^3=8$  was identified and mapped (Fig. 1). This systematic classification was applied to approximately 913 multiclassified drugs identified in our dataset. By assigning each medication to one of these eight predefined patterns, we ensured a comprehensive capture of all ATC/DDD variants. This approach significantly minimized the risk of computational errors and eliminated selection bias, ensuring high internal validity during the data harmonization phase.

## Result

Our analysis showed that, among 2,714 medications in the WHO ATC/DDD system with assigned DDD values and Adm.R, 913 drug pairs satisfied at least one of the eight classification conditions. Figure 2 illustrates the distribution of the 2,714 medications according to ATC classification, DDD, and Adm.R, as well as the frequency distribution of the 913 drug pairs across the eight-category classification framework.

For example, Olanzapine has three distinct classifications characterized by different DDD values, Adm.R, and dosage forms, including depot parenteral formulations that show in Table 1.

Table 1  
*List of different forms of Olanzapine in ATC/DDD classification*  
Considering these three distinct ATC–DDD–Adm.R–dosage form combinations, three unique pairwise combinations can be generated, as presented in Table 2. As shown, Olanzapine is the only medication that satisfies Condition 1, while the other two combinations fall under Condition 2.

| ATC     | medication | DDD | Unit | Adm.R | Note  |
|---------|------------|-----|------|-------|-------|
| N05AH03 | Olanzapine | 10  | mg   | O     |       |
| N05AH03 | Olanzapine | 10  | mg   | P     |       |
| N05AH03 | Olanzapine | 10  | mg   | P     | depot |

Table 2  
*Results of the analysis of Olanzapine that satisfy conditions 1 and 2*

| Medication | ATC1    | ATC2    | DDD1 | DDD2 | Adm.R 1 | Adm.R 2 | condition | Note1 | Note2 |
|------------|---------|---------|------|------|---------|---------|-----------|-------|-------|
| Olanzapine | N05AH03 | N05AH03 | 10   | 10   | O       | P       | 2         |       |       |
| Olanzapine | N05AH03 | N05AH03 | 10   | 10   | O       | P       | 2         |       | depot |
| Olanzapine | N05AH03 | N05AH03 | 10   | 10   | P       | P       | 1         |       | depot |

Figure 3 illustrates the frequency distribution of all drug pairs satisfying the eight classification conditions. As shown in the figure, only one molecule satisfied Condition 1, namely Olanzapine, specifically the pair consisting of immediate-release parenteral olanzapine and depot parenteral olanzapine.

As another example, Condition 6 is presented in Table 3, in which a single molecule is characterized by different ATC codes, similar DDD values, and different Adm.R.

Table 3  
The result of drugs that satisfy condition 6

| Medication           | ATC1    | ATC2    | DDD1 | DDD2 | Adm.R 1       | Adm.R 2        | condition | Note1                   | Note2                                |
|----------------------|---------|---------|------|------|---------------|----------------|-----------|-------------------------|--------------------------------------|
| Acetylsalicylic Acid | B01AC06 | N02BA01 | 1    | 1    | O             | P              | 6         | Independent of strength | Expressed as lysine acetylsalisylate |
| Betamethasone        | H02AB01 | R01AD06 | 0.4  | 0.4  | P             | N              | 6         | depot                   |                                      |
| Budesonide           | A07EA06 | R03BA02 | 1.5  | 1.5  | SL            | Inhal.solution | 6         |                         |                                      |
| Buphenine            | C04AA02 | G02CA02 | 30   | 30   | O             | P              | 6         |                         |                                      |
| Colistin             | A07AA10 | J01XB01 | 9    | 9    | O             | P              | 6         |                         |                                      |
| Cromoglicic Acid     | R01AC01 | R03BC01 | 40   | 40   | N             | Inhal.aerosol  | 6         |                         |                                      |
| Ephedrine            | C01CA26 | R03CA02 | 50   | 50   | P             | O              | 6         |                         |                                      |
| Hexoprenaline        | R03AC06 | R03CC05 | 1.5  | 1.5  | Inhal.aerosol | O              | 6         |                         |                                      |
| Hexoprenaline        | R03AC06 | R03CC05 | 1.5  | 1.5  | Inhal.aerosol | P              | 6         |                         |                                      |
| Miconazole           | A07AC01 | J02AB01 | 1    | 1    | O             | P              | 6         |                         |                                      |
| Phenylephrine        | C01CA06 | R01AA04 | 4    | 4    | P             | N              | 6         |                         |                                      |
| Vancomycin           | A07AA09 | J01XA01 | 2    | 2    | O             | P              | 6         |                         |                                      |
| Medication           | ATC1    | ATC2    | DDD1 | DDD2 | Adm.R 1       | Adm.R 2        | condition | Note1                   | Note2                                |
| Acetylsalicylic Acid | B01AC06 | N02BA01 | 1    | 1    | O             | P              | 6         | Independent of strength | Expressed as lysine acetylsalisylate |
| Betamethasone        | H02AB01 | R01AD06 | 0.4  | 0.4  | P             | N              | 6         | depot                   |                                      |
| Budesonide           | A07EA06 | R03BA02 | 1.5  | 1.5  | SL            | Inhal.solution | 6         |                         |                                      |
| Buphenine            | C04AA02 | G02CA02 | 30   | 30   | O             | P              | 6         |                         |                                      |
| Colistin             | A07AA10 | J01XB01 | 9    | 9    | O             | P              | 6         |                         |                                      |
| Cromoglicic Acid     | R01AC01 | R03BC01 | 40   | 40   | N             | Inhal.aerosol  | 6         |                         |                                      |
| Ephedrine            | C01CA26 | R03CA02 | 50   | 50   | P             | O              | 6         |                         |                                      |
| Hexoprenaline        | R03AC06 | R03CC05 | 1.5  | 1.5  | Inhal.aerosol | O              | 6         |                         |                                      |
| Hexoprenaline        | R03AC06 | R03CC05 | 1.5  | 1.5  | Inhal.aerosol | P              | 6         |                         |                                      |
| Miconazole           | A07AC01 | J02AB01 | 1    | 1    | O             | P              | 6         |                         |                                      |
| Phenylephrine        | C01CA06 | R01AA04 | 4    | 4    | P             | N              | 6         |                         |                                      |
| Vancomycin           | A07AA09 | J01XA01 | 2    | 2    | O             | P              | 6         |                         |                                      |

The complete report, including all 913 drug pairs and their corresponding classification conditions, is provided as a supplementary Excel file in the Appendix.

## Discussion

The findings of this study highlight a fundamental paradox within the ATC/DDD system. From a conceptual standpoint, the phenomenon of multiclassification is not a structural flaw but rather a deliberate design feature intended to reflect variations in dosages, strengths, and routes of administration. However, this intrinsic characteristic simultaneously acts as a source of significant ambiguity during the alignment of national drug lists (NDLs) with global standards. While the Oslo Centre provides transparent criteria for assigning new codes, there remains a clear dichotomy between the WHO's statistical objectives and the economic imperatives of national governments[1]. This challenge is further exacerbated by structural disparities between the ATC and other systems (e.g., EphMRA), rendering harmonization particularly arduous for multiclassified drugs.

A critical challenge in this field is the systemic risk of "information loss" during data mapping. Literature indicates a significant gap between the theoretical complexity of the ATC system and its practical application. For instance, while the global analysis by Chen et al. suggests that approximately 10% of medicinal products qualify as multiclassified, national registries often tend to oversimplify these complex pharmacological profiles into single code entries for administrative convenience. This discrepancy underscores a pervasive state of disharmonization[3]. In this context, the 8 Pattern Framework developed in this study serves as a robust methodological tool to identify and bridge such gaps. By providing a systematic taxonomy for these 900 potential scenarios, our framework ensures that no therapeutic identity or ATC/DDD variant is overlooked, thereby preserving the integrity of pharmaceutical data in national registries.

The high prevalence of multiclassified drugs identified in the literature suggests that these are not arbitrary administrative assignments but indicators of complex biological profiles. This perspective is reinforced by Chen et al., whose PDATC-NCPMKL-updated model demonstrated that each ATC code encapsulates a distinct biological identity defined by target proteins and structural attributes. Thus, the assignment of multiple codes is underpinned by the overlap of a drug's biological profile with diverse therapeutic classes[4]. Consequently, the suppression of valid codes for administrative simplification amounts to a negation of the drug's biological and therapeutic reality.

Furthermore, we address the internal inconsistencies of the WHO classification. As Bindel and Seifert (2025) note, the ATC system conflates contradictory criteria anatomy, therapeutic use, and chemical structure at different hierarchical levels[2]. While some advocate for a radical transition toward a mechanism-based classification, such an approach risks disrupting the continuity of longitudinal data. Therefore, this study argues that the precise identification and tagging of potential multiclassified medicines within the existing framework via the 8-Pattern Framework represents a more pragmatic and stable pathway toward international harmonization.

Finally, the necessity of recognizing all therapeutic classes extends into macro level resource management. As demonstrated by Curé (2013), oversimplifying fixed-dose combinations (FDCs) diminishes data quality. Moreover, in the context of drug shortages, overlooking code differentiation such as the distinct DDDs and therapeutic roles of aspirin as an antiplatelet (B01AC06) versus an analgesic (N02BA01) can lead to misestimated consumption volumes. Our proposed framework is designed to provide policymakers with the big picture, ensuring that NDL harmonization is not merely a technical exercise but a vital step toward regulatory consistency and optimal resource allocation[5].

## Clinical and Practical Implications: Beyond Data Mapping

The practical utility of the proposed 8-Pattern Framework extends significantly into clinical practice and hospital pharmacy management. In the era of Electronic Health Records (EHRs) and Clinical Decision Support Systems (CDSS), the precise mapping of multiclassified drugs is a prerequisite for medication safety. For instance, in Medication reconciliation processes, a failure to distinguish between different therapeutic identities of a single agent (e.g., low-dose vs. high-dose aspirin or systemic vs. inhaled corticosteroids) can trigger inappropriate drug-drug interaction alerts or, conversely, lead to the omission of critical contraindications[6].

Furthermore, from a pharmacovigilance perspective, the 8-Pattern Framework facilitates more granular signal detection. By segregating drug utilization data based on specific ATC/DDD variants, researchers can more accurately attribute adverse drug reactions (ADRs) to specific indications or administration routes. In the realm of pharmacoconomics, this level of precision is indispensable for cost of illness studies and budget impact analyses. Without the systematic tagging provided by this framework, consumption volumes for multifaceted drugs are often aggregated, leading to distorted economic models that misrepresent the true cost-effectiveness of clinical interventions.

## Strengths, Limitations, and Future Directions:

A primary strength of this study lies in its systematic approach to structural disharmonization. Unlike previous models that focus solely on ATC code discrepancies, our 8-Pattern Framework integrates three critical dimensions: the ATC code, the DDD value, and the Administrative Route. This multidimensional approach ensures a high level of internal validity and provides a reproducible protocol for other national regulatory bodies struggling with similar data heterogeneities. Moreover, the focus on potential multiclassified drugs (900 cases) provides a proactive tool for future-proofing national drug registries.

However, certain limitations must be acknowledged. First, the framework is intrinsically linked to the WHO's annual updates. As the Oslo Centre frequently revises ATC codes and DDD assignments to reflect emerging clinical evidence, the mapping results require periodic recalibration. Second, while the framework effectively categorizes conventional pharmaceuticals, its application to complex biologics and biosimilars which often possess unique nomenclature and dosing challenges may require further refinement.

Future research should focus on the computational integration of the 8-Pattern Framework into automated Mapping Algorithms. Developing a machine-learning-based tool that can automatically assign these patterns to newly registered medications would significantly reduce the manual workload of regulatory pharmacists. Additionally, expanding this methodology to include Herbal and Complementary Medicines, which are often subject to highly divergent national adaptations, represents a promising avenue for achieving a truly global standard for drug classification.

## Conclusion

In conclusion, the development of a systematic decision tree identifying eight distinct scenarios provides a robust framework for managing the complexities of multiclassified medicines within the ATC/DDD system. By successfully mapping 913 drugs through this model, this study demonstrates a viable pathway to bridge the gap between traditional classification structures and modern pharmacology. This approach not only ensures high internal validity and minimizes computational bias but also offers a scalable strategy for the harmonization of National Drug Lists. Until global structural reforms are implemented, adopting such predefined identification protocols is essential for policymakers to mitigate statistical distortion and ensure more accurate comparative analyses of drug utilization.

## Abbreviations

ATC  
Anatomical Therapeutic Chemical Classification  
DDD  
Defined Daily Dose  
Adm. R  
Administration Routes  
WHO  
World Health Organization  
NDL  
National Drug Lists

## Declarations

**Ethics declaration:** Not Applicable. This research used publicly available data from the WHO/DDD classification. No ethical approval was needed for using secondary data from a national survey.

**Consent for Publication:** Not Applicable

**Availability of Data and Materials:** The datasets are not publicly accessible but can be obtained from the author on request.

**Competing Interest Declaration:** The authors declare no non-financial interests or conflicts of interest.

**Funding Declaration:** This project has not been funded

**Financial Interest Declaration:** The authors have no financial interests to disclose.

**Author Contributions:** Study design (MV, MJR), data collection (MJR, MV), data analysis (MJR, MV), visualization (MJR), manuscript writing (MJR, MMM)

**Acknowledgements:** This paper is based on a PharmD Dissertation at Shaheed Beheshti University of Medical Science (SBMU).

## References

1. MScPharm, G. V. B. et al. P, Live Storehagen Dansie MScPharm MplICH, Kristi Henjum MScPharm P, Ignatios Ioakeim Skoufa MD, Irene Litlekare Ms, Mohammad Nouri Sharikabad MScPharm P. uidelines for ATC classification and DDD assignment. (2024).
2. Bindel, L. J. & Seifert, R. Problems associated with the ATC system of drug classification. *Naunyn-Schmiedeberg's Archives Pharmacol.* <https://doi.org/10.1007/s00210-025-04833-1> (2025).
3. Chen, L., Zeng, W. M., Cai, Y. D., Feng, K. Y. & Chou, K. C. Predicting Anatomical Therapeutic Chemical (ATC) classification of drugs by integrating chemical-chemical interactions and similarities. *PLoS One.* **7**, e35254 (2012).
4. Chen, L., Lu, Y., Xu, J. & Zhou, B. Prediction of drug's anatomical therapeutic chemical (ATC) code by constructing biological profiles of ATC codes. *BMC Bioinform.* **26**, 86 (2025).
5. Ms, C. B. et al. Hege Salvesen Blix Ms, Irene Litlekare Ms, Marit Rønning Ms, Solveig Sakshaug Ms, Hanne Strøm Ms,. Guidelines for ATC classification and DDD assignment 2013. (2013).
6. Armando, L. G., Miglio, G., de Cosmo, P. & Cena, C. Clinical decision support systems to improve drug prescription and therapy optimisation in clinical practice: a scoping review. *BMJ Health Care Inf.* ;**30**. (2023).

## Figures

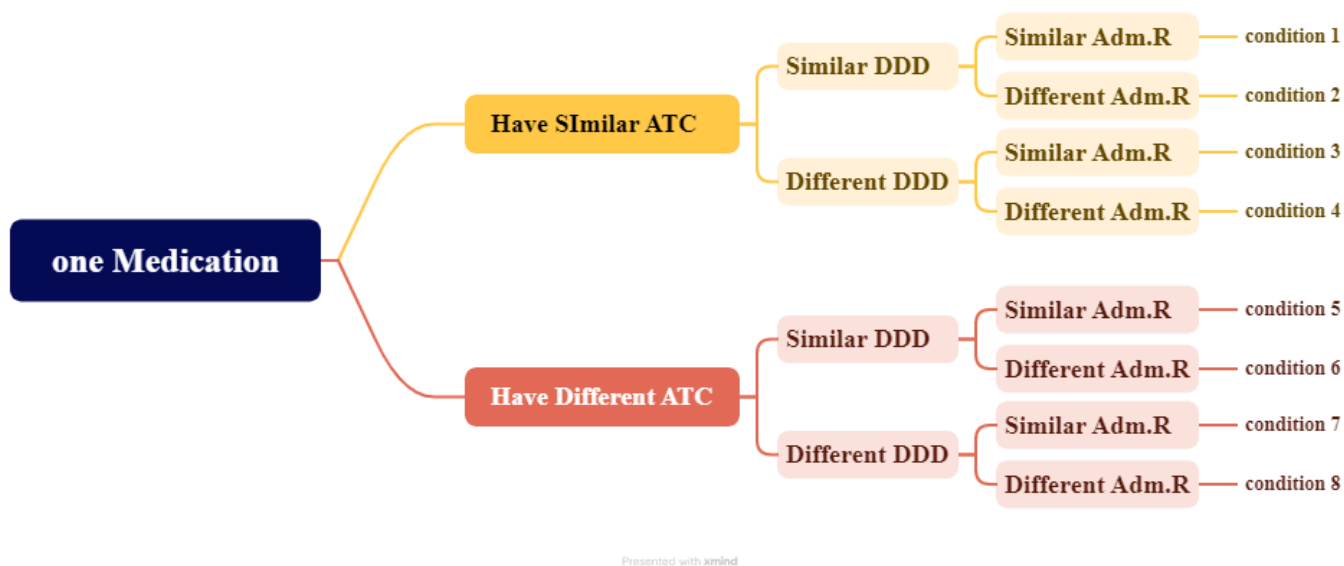


**Figure 1**

The decision tree of the model, and the 8 possible conditions that might have occurred when one drug has a different ATC classification or DDD or Adm.R

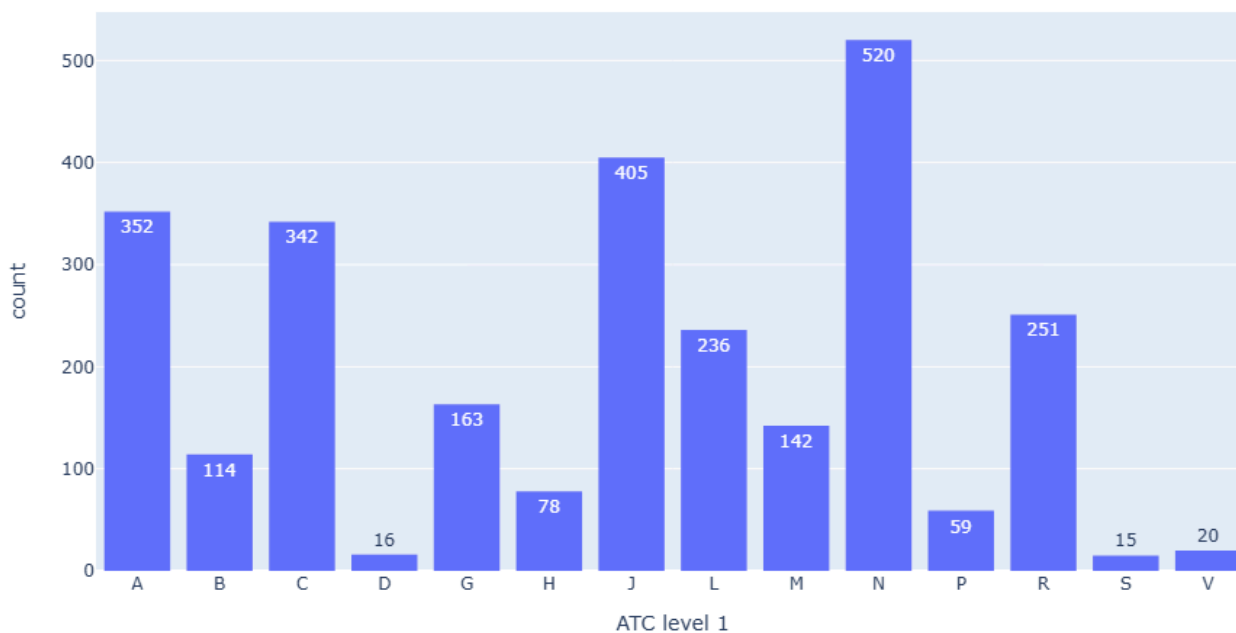


**Figure 2**

Frequency of 2714 medications have the ATC, DDD and Adm.R in WHO classifications

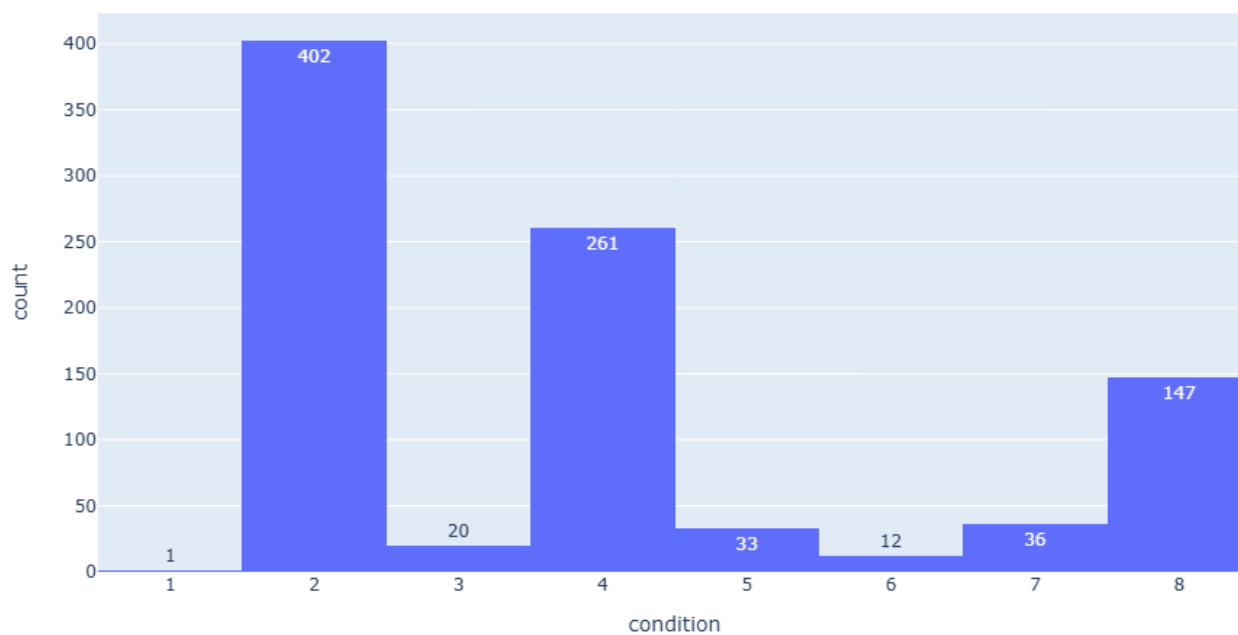


**Figure 3**

frequency of conditions

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [finalreport.xlsx](#)