# Validation of the "Indication for Use" (INDO) Variable in the Danish National Prescription Registry

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**Background:** Despite its potential value in register-based pharmacoepidemiologic research, recorded information on "indication for use" (INDO) in the Danish National Prescription Registry has rarely been used, likely because of questions about the variable's validity, which to our knowledge no study has systematically assessed.

**Methods:** We extracted data on 80,814 prescriptions from the software systems (PharmaNet and C2) of five Danish community pharmacies filled between 4 and 16 February 2019 and 2020. Using the indication information recorded in the pharmacy software systems as the gold standard, we evaluated the extent and quality of the corresponding information from the Prescription Registry.

**Results:** Of all prescriptions identified, we captured >99% in the Prescription Registry. The proportion of prescriptions with recorded indication codes in the Prescription Registry was 82% (n = 66,164) but was lower for C2 than PharmaNet. Correcting for the overrepresentation of C2 data in our sample, the estimated proportion of registration was ≈88%. Almost 100% (66,158 of 66,164) of the prescriptions with recorded indication codes in the Prescription Registry had correctly recorded indication codes. Nonspecific indication codes were present in 5.6%–36% of selected drugs and drug classes.

**Conclusions:** Prescriptions filled at Danish community pharmacies are accurately captured by the Danish National Prescription Registry, and the recorded information on indication is generally valid and usable in research. However, minor concerns remain about missingness, nonspecific recorded indication codes, and lower validity, and a higher proportion of missingness of recorded indication codes is expected before 2017.

**Keywords:** Drug Prescriptions, Danish National Prescription Registry, Epidemiology, Indication, Pharmacies, Pharmacoepidemiology, Validation Study

***(Epidemiology*** 2024;35: 1–6)

*A supplementary digital video by the article's co-author, Hanin Harbi, is available at http://links.lww.com/EDE/C89*

Submitted March 29, 2023; accepted August 18, 2023

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The authors report no conflicts of interest.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

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ISSN: 1044-3983/24/351-16

DOI: 10.1097/EDE.0000000000001666

Denmark has a long tradition of register-based pharmacoepidemiologic research, with the main data source being the Danish National Prescription Registry, a nationwide register collecting individual-level data on all prescriptions redeemed at Danish community pharmacies since 1995. The data originate from the pharmacy software systems and include variables related to the drug, patient, prescriber, and pharmacy.[1] Despite its contributions to the understanding of the utilization, efficacy, and safety of drugs, the Prescription Registry remains underutilized. One such example is data on the underlying indication for the use of a given drug, which, although recorded in the registry, is hardly ever used. This is likely explained by the validity of these data having been questioned. However, no studies have systematically evaluated the quality of this variable in the registry. Since electronic prescribing in 2017 became mandatory in Denmark,[2] and as the use of electronic prescriptions was considerable also before this point, one might expect that the information on indication is increasingly well captured. The possibility of using indication information from the Prescription Registry could open up a range of new opportunities for Danish pharmacoepidemiology. Therefore, the aim of this study was to assess the validity of the indication information recorded in the Prescription Registry.

## METHODS

This validation study was performed based on prescriptions dispensed at five Danish community pharmacies during two time periods. To assess the extent and quality of the indication information recorded in the Prescription Registry, the information recorded in the Prescription Registry was compared with that in the label texts abstracted from the pharmacy systems.

## SETTING

In Denmark, electronic prescribing became mandatory by law on 1 October 2017. Since then, paper, fax, and telephone prescribing have only been allowed in special circumstances, that is, when electronic prescribing is not possible.[2] When issuing an electronic prescription, the prescriber can select an indication from a drop-down menu of prespecified, approved indications for the specific drug, in which case an indication code is recorded in the Prescription Registry. The

selected indication is converted to text, which can be edited by both the prescriber and pharmacy staff. The prescriber can also enter the indication manually. In these cases, the indication information is not transferred from the pharmacy systems to the Prescription Registry.[3]

## DATA SOURCES

Danish community pharmacies record data on all dispensed prescriptions in their software systems.[1] At present, three different pharmacy systems are available: PharmaNet, C2, and Apoteksdata. About three-quarters of Danish community pharmacies use PharmaNet, about a quarter use C2, and only a few use Apoteksdata.[4] In this study, we included one community pharmacy from each of the five Danish regions, of which two used PharmaNet and three used C2. We obtained community pharmacy prescription data from the software suppliers; these data included the label texts containing the desired indication information.

The Prescription Registry has received data on prescription fills from community pharmacies throughout the country since 1995. Its main purpose is to enable continuous monitoring of the use of drugs in Denmark.[1] In the Prescription Registry, the indication is recorded in the variable designated "indication for use" (INDO).[3] In this study, data from the Prescription Registry were obtained via Statistics Denmark. We considered the indication information recorded in the pharmacy systems (i.e., the package labels) as the gold standard against which the validity of the information from the Prescription Registry was evaluated.

All data were linkable via a unique person ID, the Central Person Register number, assigned to all Danish residents since 1968.[5]

## DATA MATERIAL

The study was based on data extracted from the software systems of the five community pharmacies on all prescriptions dispensed during the randomly selected period from 4 to 16 February in 2019 and 2020. As a rule, the software suppliers do not store data for more than 2 years. One of the two pharmacies using PharmaNet failed to provide data for 2019. We extracted prescription data for the same individuals during the same time periods from the Prescription Registry by Statistics Denmark and via the unique person ID.

To identify prescriptions from each data source that were eligible for unambiguous linkage, we introduced three exclusion steps. First, we excluded prescriptions dispensed by invalid person IDs. Second, to eliminate prescriptions for drugs recorded in an unsystematic manner (most notably magistral drugs), records of nondrugs (e.g., food supplements and medical devices), and fees, we excluded records with missing or invalid Anatomical Therapeutic Chemical (ATC) codes and/or non-Nordic article numbers (i.e., outside the range of 000001–199999 and 370000–599999).[6] Third, we excluded dispensings happening more than once in a given day, that is, records with the same person ID, dispensing date, and ATC code.

We linked prescriptions from the pharmacy systems to their counterparts from the Prescription Registry using the person ID, dispensing date, and ATC code and excluded prescriptions found in only one of the two data sources.

## VALIDATION

The linked prescriptions fell into two groups based on the presence or absence of an indication recorded in the Prescription Registry.

For prescriptions with recorded indications in the Prescription Registry, we compared the indication information from the two data sources in a three-step matching process:

The first step was an automatic search of the label text for the exact indication recorded in the Prescription Registry. However, the label text could in principle contain more indication information than recorded in the Prescription Registry. For a random sample of 200 automatic matches, we therefore "subtracted" the indication recorded in the Prescription Registry from the label text and manually screened the rest of the label text for additional, uncaptured indication information.

The second step consisted of exploring the 50 most frequent unmatched combinations of label texts and recorded indications in the Prescription Registry to identify and account for recurrent pairs of nonidentical but nevertheless similar indications.

The third step involved the manual review of remaining prescriptions for matching indications. To be considered a match, the indications should have the same meaning despite being spelled or phrased differently.

For prescriptions with no recorded indication in the Prescription Registry, we manually evaluated the label text for the presence of any indication information for a random sample of 500 prescriptions.

We originally planned to also validate the recorded dosages in the Prescription Registry. However, the recording of this information in the Prescription Registry was negligible (0.06%), and thus we did not find it meaningful to validate the dosage information further.

## ANALYSES

Our main outcomes were the proportion of prescriptions with recorded indications in the Prescription Registry and the correctness of recorded indications in the Prescription Registry. Correctness of recorded indications in the Prescription Registry was defined as the proportion of prescriptions with correctly recorded indications in the Prescription Registry of all prescriptions with recorded indications in the Prescription Registry. Correctness of an absent indication was defined as the proportion of prescriptions with correctly absent indications in the Prescription Registry of the 500 randomly selected prescriptions with absent indications in the Prescription Registry.

We tested our hypothesis that the registration of indication information has improved over time by stratifying the proportion of prescriptions with absent indications in the Prescription Registry by time period (2019 and 2020).[2] To detect differences between pharmacy systems and drug classes, we also stratified by pharmacy system (PharmaNet and C2) and by the first level of the ATC code (i.e., the target organ or system), respectively.

To exemplify challenges with using the indication information recorded in the Prescription Registry in register-based pharmacoepidemiologic research, we performed a supplementary analysis where we reported the eight most frequently recorded indications in the Prescription Registry for three common drugs and drug classes with several therapeutic uses: beta-blockers (ATC code: C07), phenoxymethylpenicillin (ATC code: J01CE02), and selective serotonin reuptake inhibitors (SSRIs) (ATC code: N06AB). For the same three drugs and drug classes, we described the distribution of indications according to the pharmacy system when restricting to prescriptions where no indication information was recorded in the Prescription Registry.

## OTHER

All analyses were performed using STATA 17 (StataCorp, College Station, TX). In terms of data protection, the study was registered at the University of Southern Denmark's inventory (record no. 11.093). In Denmark, ethical approval is not required for purely register-based studies.

## RESULTS

From a total of 91,233 and 94,703 prescriptions obtained from the pharmacy systems and Prescription Registry, respectively, we excluded 28 and 0 prescriptions with invalid person IDs, 1,698 and 1,215 prescriptions with missing or invalid ATC codes and/or non-Nordic article numbers, and 8,153 and 4,663 prescriptions with multiple daily dispensings, resulting in 81,354 and 88,825 prescriptions eligible for linkage. Of those eligible for linkage, 80,814 occurred in both data sources

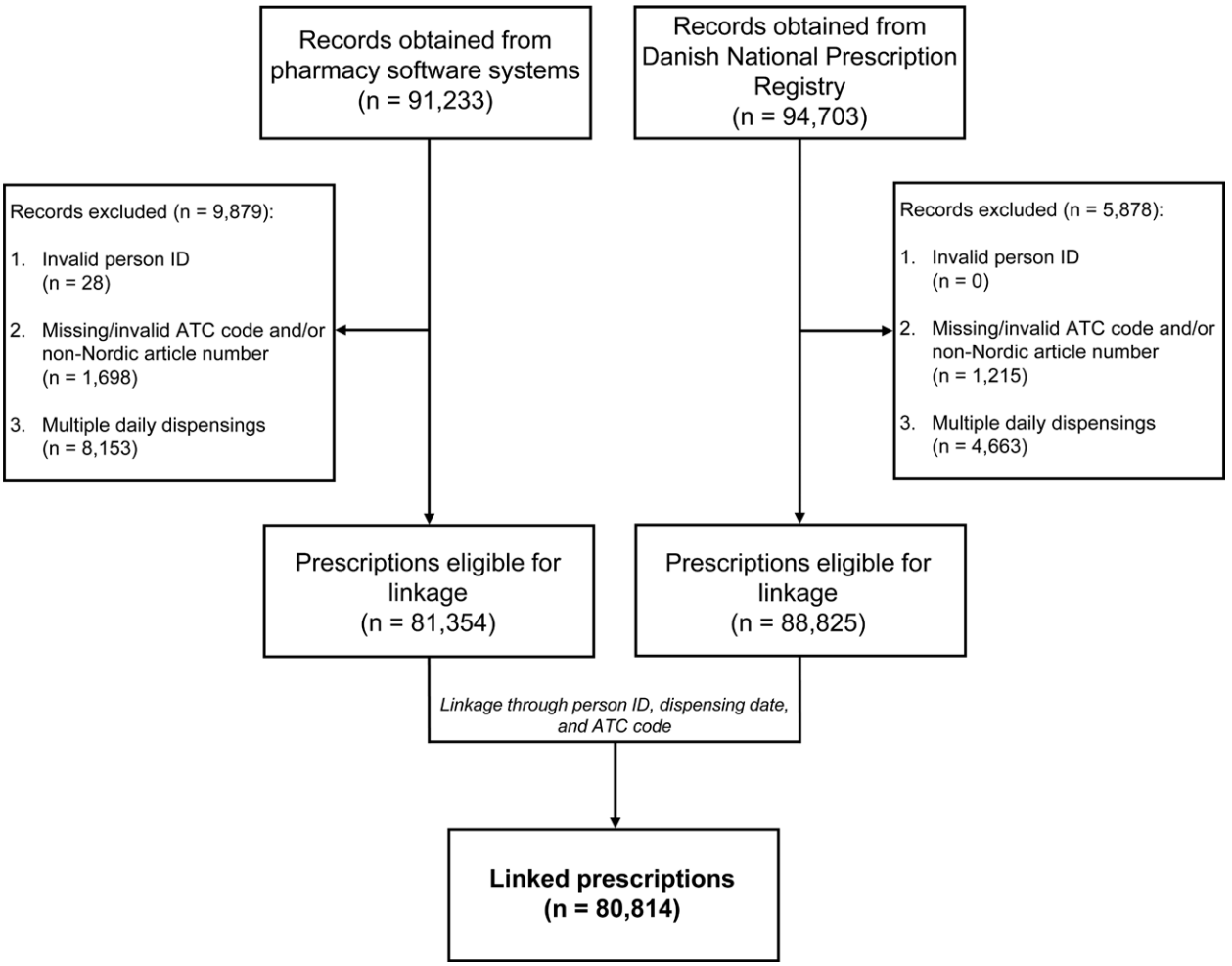


**FIGURE 1.** Flowchart describing the identification and selection of prescriptions to be matched between data obtained from the pharmacy software systems and records identified in the Danish National Prescription Registry.

and were therefore linked (**Figure 1**). Only 0.66% (540) of the prescriptions from the pharmacy systems were not identifiable in the Prescription Registry. Conversely, 9.0% (8,011) of the prescriptions from the Prescription Registry were not recorded in the pharmacy systems. These missing prescriptions in the pharmacy systems can, however, be explained by the fact that the data extracts from the Prescription Registry were based on the person IDs recorded in the pharmacy systems during the study periods and therefore not pharmacy-specific.

Of the linked prescriptions, 82% (66,164) had an indication recorded in the Prescription Registry. In terms of the correctness of recorded indications in the Prescription Registry, the exact indication recorded in the Prescription Registry occurred in the label text for 97% (64,232) of the prescriptions with recorded indications in the Prescription Registry. For all 200 randomly selected automatic matches, the Prescription Registry had captured all indication information in the label text, and the indication recorded in the Prescription Registry was therefore identical to that in the label text. The most frequent pairs of nonidentical but similar indications turned out to be "mod sukkersyge"/"mod diabetes" ("against glucose disorder" [a common Danish lay term for diabetes]/"against diabetes") and "forebyggende mod hjertekarsygdomme"/"forebyggelse af hjertekarsygdomme" ("preventive against cardiovascular diseases"/"prevention of cardiovascular diseases"). These two specific discrepancies constituted 2.9% (1,912) of the prescriptions with recorded indications in the Prescription Registry. The remaining 0.03% (20) showing discrepancies were reviewed manually. Of these, 70% (14) had matching indications. Thus, virtually 100% (66,158 of 66,164) of the prescriptions with recorded indications in the Prescription Registry had correctly recorded indications in the Prescription Registry (**Table 1**).

In terms of the correctness of absent indications in the Prescription Registry, only 3.2% (16) of the 500 randomly selected prescriptions with absent indications in the Prescription Registry did not contain any indication information in the label text and thus had correctly absent indications in the Prescription Registry (**Table 1**).

The extent of recorded indications in the Prescription Registry varied over time and pharmacy system (**Table 2**). Overall, the proportion of prescriptions with absent indications in the Prescription Registry decreased over time (from 20% in 2019 to 17% in 2020) and was higher for C2 than PharmaNet (23% compared with 9.2%). The extent of recorded indications in the Prescription Registry also varied according to drug class (**eTable 1**; http://links.lww.com/EDE/C60) with the highest proportions of absent indications in the Prescription Registry among prescriptions related to blood and blood-forming organs (28%), antineoplastic and immunomodulating agents (27%), and the lowest among those related to anti-infectives for systemic use (7.8%) and sensory organs (8.2%).

The supplementary analysis of the top eight recorded indications in the Prescription Registry for selected drugs or drug classes revealed the presence of nonspecific indications.

**TABLE 1.** Proportion of linked prescriptions with (in)correctly recorded indications in the Danish National Prescription Registry of all linked prescriptions with recorded indications in the Danish National Prescription Registry and proportion of linked prescriptions with (in)correctly absent indications in the Danish National Prescription Registry of the 500 randomly selected linked prescriptions with absent indications in the Danish National Prescription Registry.

| | Recorded Indication | |
|---|---|---|
| **Correctness** | **Yes** | **No** |
| Correct | 100% (66,158/66,164) | 3.2% (16/500) |
| Incorrect | 0.01% (6/66,164) | 96.8% (484/500) |

**TABLE 2.** Proportion of linked prescriptions with no recorded indication in the Danish National Prescription Registry overall and stratified by time period and pharmacy software system.

| | Pharmacy Software System | | |
|---|---|---|---|
| **Time Period** | **All** | **PharmaNet** | **C2** |
| All | 18% | 9.2% | 23% |
| 2019 | 20% | 10% | 24% |
| 2020 | 17% | 8.6% | 23% |

For beta blockers, 13% of the recorded indications in the Prescription Registry were nonspecific and included "for hjertet" ("for the heart") (11%) and a combined group of less frequent indications named "Other" (1.7%) (**eTable 2**; http://links.lww.com/EDE/C60). The corresponding proportion for phenoxymethylpenicillin was 36% and included "mod infektion" ("against infection") (18%) (also the most frequent recorded indication for this drug), "mod betændelse" ("against inflammation") (15%), and "Other" (2.5%) (**eTable 3**; http://links.lww.com/EDE/C60), and for SSRIs 5.6% and included "nervemedicin" ("nerve medicine") (**eTable 4**; http://links.lww.com/EDE/C60).

For the same three drugs or drug classes, the distribution of indications was generally similar among prescriptions with no recording of the indication in the Prescription Registry (**eTable 5–7**; http://links.lww.com/EDE/C60) compared with prescriptions with a recorded indication (**eTable 2–4**; http://links.lww.com/EDE/C60).

## DISCUSSION

In this validation study of the INDO variable in the Prescription Registry, we compared indication information from the Prescription Registry with indication information in label texts from pharmacy software systems. We found that prescriptions filled at Danish community pharmacies could reliably be found in the Prescription Registry and that recorded indications in the Prescription Registry are currently highly valid. However, some prescriptions had no recorded

indications in the Prescription Registry and further, a considerable proportion had nonspecific indications recorded.

The main strengths of our study are the large number of prescriptions included from five different community pharmacies, each representing one of the five Danish regions, in two different years, and the fact that it also serves as a general validation of the Prescription Registry. More than 99% of the included prescriptions from the pharmacy systems are recorded in the Prescription Registry under the correct person ID, dispensing date, and ATC code, thereby supporting that the Prescription Registry has a complete capture of prescriptions filled in Danish community pharmacies.[1] Our study also has several weaknesses. First, it is not representative of the distribution of software systems across Danish community pharmacies. In Denmark, the most frequently used pharmacy systems are PharmaNet and C2, with about three-quarters of community pharmacies using PharmaNet and about a quarter using C2.[4] Our study included three C2 pharmacies and two PharmaNet pharmacies, with one of the PharmaNet pharmacies providing prescription data for only one of the two study periods. In other words, C2 was overrepresented, and since we observed a higher proportion of prescriptions with absent indications in the Prescription Registry for C2 than PharmaNet, this means that the actual average level of recorded indications in the Prescription Registry is higher than our overall estimate. Correcting for the overrepresentation of C2, the estimated proportion of prescriptions with recorded indications in the Prescription Registry is ≈88%. Second, we could not obtain prescription data from before 2019. The INDO variable was introduced in 2004/2005. The utility of the variable is expected to be closely related to the proportion of prescriptions issued electronically. We expect the proportion of prescriptions with recorded indications in the Prescription Registry as well as the correctness (i.e., validity) of the recorded indications to increase with the proportion of electronic prescriptions, as this will mean less manual entry of indication information. Therefore, the validity of the variable is expected to have increased steadily from 2004/2005 to 2017 and to be very high (i.e., correspond to the value reported in this study) from 1 October 2017, when electronic prescribing became mandatory in Denmark.[2] Third, we excluded magistral drugs, to which our results cannot necessarily be extrapolated. The unsystematic registration of prescription data observed for magistral drugs can be expected to lead to a decrease in both the extent and quality of recorded indications in the Prescription Registry. Fourth, we also excluded prescriptions with multiple daily dispensings, thereby assuming that the validity of the indication information recorded in the Prescription Registry does not depend on the number of daily dispensings of a prescription. However, we expect this assumption to be reasonable and thus unlikely to affect our results.

To our knowledge, the indication information recorded in the Prescription Registry has not been validated before. However, it has been used, albeit to a limited extent, in Danish pharmacoepidemiologic research. Examples of use include identification of study populations,[7] characterization of patterns and trends in prescription and use of drugs, for example, to examine the indications for prescription of specific drugs or the drugs prescribed for specific indications,[8] and estimation of prevalence and incidence.[9]

The demonstrated validity of recorded indications in the Prescription Registry renders them usable in register-based pharmacoepidemiologic research. However, when using the indication information recorded in the Prescription Registry, a number of things should be taken into consideration. First, the vast majority of absent indications appear to be incorrectly absent. Second, recorded indications may be nonspecific, for example, "for the heart" for beta blockers. Whether nonspecific indications are useful in a given pharmacoepidemiologic study depends on the research question: If the aim is, for example, to examine the indications for prescribing beta blockers, the nonspecific indication "for the heart" is of no value and can be considered missing. However, if the variable is used to either identify or exclude prescriptions of beta blockers for tremor, the nonspecific indication "for the heart" remains highly useful. Third, the validity of recorded indications is unknown before 2019 but is expected to increase gradually up to and remain high from 1 October 2017 onwards, corresponding to the increasing proportion of electronic prescribing. Fourth, the fact that recorded indications are validly captured does not necessarily mean that the prescribers entered the correct indications. Although we could not quantify the proportion of incorrect indications, it is likely not a rare phenomenon and may in part be explained by the use of drop-down menus rather than manual entries. Fifth, the validity of recorded indications is unknown for magistral drugs.

In conclusion, we found that the indication information recorded in the Prescription Registry is currently valid, providing opportunities for future use in register-based pharmacoepidemiologic research.

## ACKNOWLEDGMENTS

*We thank Aalborg Nørresundby Pharmacy, Aarhus Marselisborg Pharmacy, Ejby Pharmacy, Hvalsø Pharmacy, and Copenhagen Sønderbro Pharmacy for their participation and cooperation. We also thank Peter Bjødstrup Jensen and Morten Olesen from the University of Southern Denmark for their valuable help with data management.*

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