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Associations between use of antibiotic and non-antibiotic drugs on the gastrointestinal carriage of *Klebsiella pneumoniae* in a general adult population in Norway

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I would like to dedicate this thesis to my parents and my older brother for always being there for me.

Truong An Le

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Abbreviations

AMR	Antimicrobial Resistance
ATC	Anatomical Therapeutic Chemical
DDD	Defined Daily Dose
FK	Felleskatalogen
K. pneumoniae	*Klebsiella pneumoniae*
NLH	Norsk Legemiddelhåndbok
NorPD	Norwegian Prescription Database
OTU	Operational Taxonomic Units
PDC	Proportion of Days Covered
PPI	Proton-pump Inhibitor
T1DM	Type 1 Diabetes mellitus
T2DM	Type 2 Diabetes mellitus
WHO	World Health Organization

Abstract

Antimicrobial resistance has long been a problem and a struggle to compromise as life-threatening infections are harder to treat. Among common pathogens, *Klebsiella pneumoniae* (*K.pneumoniae*) can be a highly resistant bacteria associated with increased mortality when infecting critically ill and immunocompromised patients. Prevalence of gastrointestinal carriage depends on several risk factors. Hospital stays and antibiotic use have been associated with *K. pneumoniae* carriage in the past, and several researchers have investigated how non-antibiotic drug use can alter the gut microbiome. Few have investigated non-antibiotic drug use as a potential risk factor. In this study we investigated if the use of antibiotic, non-antibiotic drugs and a combination of drugs can affect the gastrointestinal carriage of *K. pneumoniae* in terms of total exposure in defined daily dose (DDD), daily dosage and time of drug use. Our study population consisted of 2,997 participants aged ≥ 40 years from the seventh wave of the Tromsø Study: Tromsø 7 (2015-2016). Drug use data was acquired from the Norwegian Prescription Database (NorPD) and linked with data from Tromsø 7. We constructed treatment episodes with an allowed gap of 14 days and an assumption of 80% adherence and used logistic regression to analyze the different drugs as risk factors. We included the past six months for non-antibiotic and past two months for antibiotics in the analysis. Antacids (adjusted odds ratio 1.004, 95% Cl 1.001-1.006), antibiotics (1.027, 1.004-1.049), increasing age (1.016, 1.005-1.028), diabetes mellitus (2.467, 1.423-4.274) and Crohn's disease/ulcerous colitis (2.367, 1.281-4.406) were factors based on total drug use exposure in DDD. As for daily dosage, antibiotics (1.949, 1.301-2.920), increasing age (1.018, 1.007-1.030) and having Crohn's disease/ulcerous colitis (2.355, 1.271-4.363) were risk factors. We used a Venn diagram to illustrate the prevalence of carriage when a combination of drugs was used. The prevalence increased among those using two drugs and decreased when using three drugs of antacids, anti-inflammatory/antirheumatic drugs and antibiotics. Cumulative change graphs were used to illustrate the relationship between prevalence of carriage and last use of a drug group for the preceding 12 months. Antacid, thyroid drug, anti-inflammatory/antirheumatic drug and antibiotic users had a higher prevalence of *K. pneumoniae* carriage than the non-users, and the prevalence decreased for each month between last use of a drug group and fecal sample taken.

1 Introduction

Antimicrobial resistance (AMR) is considered one of the biggest threats to global health (1). Today, at least 50,000 people die each year from drug-resistant infections in Europe and US alone. Including the rest of the world this number might increase to at least 700,000 people each year. In 2050, this number is projected to increase to 10 million people dying with economical costs up to 100 trillion USD (2). Due to this critical situation, the need for new antimicrobial agents is crucial. However, fewer antimicrobial agents have been developed over the years. A study based on data from the United States Food and Drug Administration databases (FDA), found a 56% decreased FDA approval of new antimicrobial agents over the past 20 years from 1983 to 2002 (3).

Among all the various bacteria, *Klebsiella pneumoniae* (*K.pneumoniae*) stands out as one of the major threats due to its high frequency of AMR genes, and potential to spread and acquire these genes (7). A study has shown that *K. pneumoniae* harbored up to the double amount of AMR genes compared to other gram negative bacteria (*A. baumannii*, *P. aeruginosa*, *E. cloaceae* and *E.coli*) (4).

K. pneumoniae is a gram-negative bacterium and is included in the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter*), that causes most nosocomial infections throughout the world. The ESKAPE pathogens apart from *S. aureus* are considered dangerous for critically ill and immunocompromised patients but are otherwise not pathogenic (4). The ESKAPE pathogens are considered dangerous because of their several mechanisms, including their potential to transfer and accumulate AMR through horizontal gene transfer (HGT).

Limited antibiotics to treat high-resistant infections in these patients could result in a high mortality rate. A systematic review and meta-analysis conclude that *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* infection-related mortality is high. 37 studies were taken into account for the meta-analysis and showed an overall mortality rate of 41.0%, with the highest mortality rates being observed in oncology patients (56.0%) and in Brazil, 51.3% as opposed to other countries (5).

K. pneumoniae carriage is common on mucosal surfaces in humans such as the intestinal tract, nasopharynx and oropharynx. The carriage of *K. pneumoniae* in fecal samples ranges from a minimum 5 to 38%, while the carriage in the nasopharynx ranges from 1 to 6% (6). The carriage rate varies from study to study depending on prevalence of risk factor. Previous studies have identified antibiotic use, hospitalization, alcohol consumption, smoking and comorbidities such as chronic obstructive pulmonary disease (COPD) as risk factors for being a carrier (7–9).

There is currently one published study that has examined specifically if non-antibiotic drugs are considered as risk factors for *K. pneumoniae* carriage (10). There are also several published studies examining the association between non-antibiotic drugs and change in the gut microbiome. This change could potentially influence the carriage of *K. pneumoniae.*

A microbiome is a community of microorganisms (bacteria, fungi, virus) living together in a specific habitat. Humans have several microbiomes such as the skin, oral cavity, nasal cavity and the gastrointestinal tract. The number of microorganisms can be reduced and increased by the drug use. Other non-drug factors such as diet, genetics, diseases and method of childbirth delivery can also affect the gut microbiome (11,12).

Antidiabetics alter the gut microbiome. In a study by Forslund et al. data from 784 human gut metagenomes were analyzed to evaluate the effect of metformin has on the gut microbiome composition. The metagenomic dataset included type 1 diabetes mellitus (T1DM) patients, type 2 diabetes mellitus (T2DM) patients, and non-diabetic participants as controls from cohorts in Denmark, Sweden and China (13). Treatment with metformin significantly increased *Escherichia* and lowered *Instestinibacter* abundance.

Another efficacious treatment for T2DM are the α-glucosidase inhibitors such as acarbose. In a randomized, double-blind, controlled crossover trial by Zhang et al. the human gut composition was explored before and after treatment with α-glucosidase inhibitors in patients with prediabetes. Fifty-two participants were enrolled with a prediabetes diagnosis according to World Health Organization (WHO) criteria 1998. The participants were randomly placed in two treatment sequences starting with a 4 weeks treatment of either α-glucosidase inhibitors or placebo. A total of 108 genera were identified, and as close as 40% (43 genera) were at a relatively higher abundance after acarbose treatment. At genera level, treatment with acarbose

increased the abundance for five genera, including *Lactobacillus* and *Dialister*. In contrast, six genera were observed as having a lower abundance after acarbose treatment, such as *Butyricicoccus*, *Phascolarctobacterium*, and *Ruminococcus* (14).

The influence of non-steroidal anti-inflammatory drugs (NSAIDs) on the gut microbiome were examined in a study done by Rogers and Aronoff (15). These researchers recruited 155 participants aged ≥18 years from southeastern Michigan in the USA. The participants completed questionnaires involving demographic characteristics, medical history, diet and drug use the past 30 days. Controls were defined as not using any drugs the past 30 days. Different NSAIDs were found to be associated with distinct microbial populations. Users of aspirin were discriminated from the non-drug users by four Operational taxonomic units (OTUs) (*Prevotella spp.*, *Bacteroides spp*, an OTU from family *Ruminococcaceae*, *Barnesiella spp*.). The study also concludes that the microbiome profile of celecoxib was similar to ibuprofen users, with both increasing the abundance of *Acidaminococcaceae* and *Enterobacteriaceae.* However, result of celecoxib are questioned by others (16).

A study examined the association between proton-pump inhibitors (PPI) usage and the altering of the gut microbiome composition in 1827 healthy twins. PPI use was self-reported and several confounders were adjusted for. The results from the study pointed toward several positive and negative associations between PPI use and the specific taxonomic abundances. The order *Lactobacillales*, and in particular the family *Streptococcaceae* had the strongest positive association. The families *Lachnospiraceae* and *Ruminococcaceae* had the strongest negative association (17).

Other researchers examined the association between PPI usage and altering of the gut microbiome in three independent cohorts and matched controls from the Netherlands. Cohort 1 is a population cohort, cohort 2 are patients with inflammatory bowel disease (IBD) and cohort 3 are patients with irritable bowel syndrome (IBS). These cohorts together comprise of 1815 participants. The data is analyzed individually in each cohort, and thereafter a meta-analysis of the three cohorts. Factors that might affect the gut microbiome were adjusted for each individual cohort. The meta-analysis showed statistically significant changes in 92 of the 460 bacterial taxa abundances (18).

Both studies hypothesize that PPIs alter the gut microbiome composition through their direct effect on stomach acid. The acid acts as a defense mechanism against bacteria with bad tolerance against low pH. Treatment with PPIs will increase pH and therefore weaken the defense mechanism. This will allow commensal bacteria of the oral area to colonize further down the gastrointestinal tract and be detected in fecal samples. Both studies discovered an increased abundance of oral commensals in the gut microbiome composition after PPI use (17,18).

Several commonly used drugs were examined if they had an impact on the gut microbial composition using the same dataset mentioned above (18). Difference between users and non-users were examined for each cohort, and thereafter a meta-analysis of all three cohorts. PPI, metformin, antibiotics and laxatives had the largest number of associations with altering the gut microbiome after adjusting for multiple drugs being used at the same time (19).

In a cross-sectional study by Flowers et al. 117 patients with bipolar disease (BD) had their fecal sample analyzed. They were separated by atypical antipsychotic use (AAP) and non-AAP use. AAP users had a significant reduced microbiome diversity compared to the non-AAP users. When stratified after gender, female AAP users had an even greater reduced diversity compared to female non-AAP users. Male AAP users had a non-significant difference in microbiome diversity compared to male non-AAP users, but that might be due to the few male participants in the BD cohort (20)

Currently, there is one published study from University Hospital of North Norway (UNN) and University of Tromsø (UiT) examining specifically if the use of both antibiotics and non-antibiotic drugs are associated with gastrointestinal carriage of *K. pneumoniae* (10). This master project is based on the same dataset as this study. The dataset originates from a linkage between NorPD, the Norwegian national prescription register, and the 7th wave of the Tromsø Study, a population-based study of persons aged 40 and older in Tromsø, Norway.

Due to the severe complications caused by *K. pneumoniae* and a few to none previous studies examining the associations between non-antibiotic drug use and *K. pneumoniae* carriage, makes this a good reason to explore the unknown. The combination of the Tromsø survey and NorPD gives us a unique opportunity to study how carriership of *K. pneumoniae* is associated with the use of medications in a general adult population.

2 Study aims

- To examine if the use of individual drug groups are associated with *K. pneumoniae* gastrointestinal carriage
    - Examine if total exposure in defined daily dose (DDD) of a drug group is associated with *K. pneumoniae* gastrointestinal carriage
    - Examine if the time of drug use (last use of a drug group) is associated with *K. pneumoniae* gastrointestinal carriage
    - Examine if daily dose drug use is associated with *K. pneumoniae* carriage
- To examine how combinations of drug groups influence the *K. pneumoniae* gastrointestinal carriage

3 Methods and materials

3.1 Data sources

3.1.1 Tromsø 7

The Tromsø study consists of seven repeated surveys conducted over a long period from 1974 to 2016, in the municipality of Tromsø, Norway (21). It was initiated in 1974 with the primary target to combat the high mortality of cardiovascular diseases in Norway that was often occurring among middle-aged men. In the recent surveys, the Tromsø study has put more emphasis on many other diseases and conditions like diabetes mellitus and osteoporosis (22).

The seven Tromsø surveys (referred as Tromsø 1-7) include questionnaires, biological sampling and physical examinations. The questionnaires cover a broad range of issues related to diseases, health, lifestyle, family, diet and other topics depending on the aims of each survey.

After completing the questionnaires, the participants were invited to a physical examination. In Tromsø 1, the participants' blood pressure, height and weight were measured. In the later surveys as Tromsø 4-6, new physical examinations have been included. Example of those are measurement of hip and waist measurement (22).

A second visit for physical examinations were established in Tromsø 4 and included in the later surveys. The physical examinations included ultrasound of carotid artery, echocardiography, bone densitometry of the hip (dual-energy X-ray absorptiometry, DEXA) and spirometry (22).

Collection of fecal samples were first established in Tromsø 7 for second visit participants. Sampling kits were given out to participants to collect fecal samples, which were sent to a laboratory for screening (23).

Tromsø 7 was conducted in March 2015-October 2016. Only citizens ≥40 years in municipality Tromsø, Norway were invited to participate in the survey. The participants had to complete the two standard questionnaires which covered health, diet, lifestyle, ethnicity, family and traveling abroad. The questionnaires and the full details on the survey can be found in the web page of University of Tromsø – The Arctic University of Norway (23).

All participants went through basic examination at their first clinical screening visit. The examinations consisted of anthropometric measurements (height, weight, waist and hip circumference), blood pressure, heart rate, oxygen saturation and biological sampling.

A predefined sample of about 13 000 people were invited for a second visit. The participants from the first visit were randomly selected to the second visit. Former Tromsø study participants (From Tromsø 6) who completed their previous second visit were added to this predefined sample. The participants were required to go through more blood sampling and other tests. They also received equipment to collect fecal samples. These samples were sent to a laboratory for screening for *K. pneumoniae* carriage

A list of variables to be used is in the appendix. The main outcome measure will be carriage of *K .pneumonia* while the other variables will be used to control for confounding and validation and augmentation of NorPD information about drug use.

3.1.2 NorPD

NorPD is a national drug register based on prescriptions dispensed at Norwegian pharmacies. The main objectives of the register are as defined by the authoritative regulations, to collect and prepare data on drug use in order to (24):

- Describe the drug use pattern and the changes over time.
- Encourage and give a basis for research and investigation, in order to explain the positive and negative effects of drug use.
- Give the authorities quality assurance on drug use, surveillance, control and planning.
- Give the prescribers a basis for internal control and a potential improving quality in prescribing practices.

To achieve these objectives the authoritative regulations have defined which data are needed. The data included in each record are as follows (24):

- Patient information: sex, year/month of birth, year/month of death and address
- Prescriber information: sex, year of birth, profession and specialty
- Drug information: product and package size, number of packages, category of prescription, Anatomical Therapeutic Chemical (ATC), Defined Daily Dose (DDD), reimbursement code, price, dispense date
- Pharmacy information: License and organization number, municipality

Data from NorPD will be used to assess the participants' drug use the past 12 months before the date of the fecal screening. Only the necessary data such as when the prescriptions were dispensed (defined as drugs used), product and package size, number of packages, ATC, DDD and patients' data from Tromsø 7 will be used for the statistical analyses.

3.2 Study population

Our study population is a sample drawn from a source population. The source population will be included in this study to compare with our study population in terms of demographic characteristics and drug use.

The source population consist of all participants who attended the Tromsø 7 study. Only participants > 40 years old in municipality Tromsø were invited. The attendance rate was 65% (n=21,083) which included 10,009 men (47%) and 11,074 women (53%). The mean age for the source population is 57 years. The NorPD dataset contains a total of 259,394 prescriptions in the period from 1. January 2014 to 31 December 2016, in which men have filled 97,035 prescriptions (37%) and women have filled 162,359 prescriptions (63%).

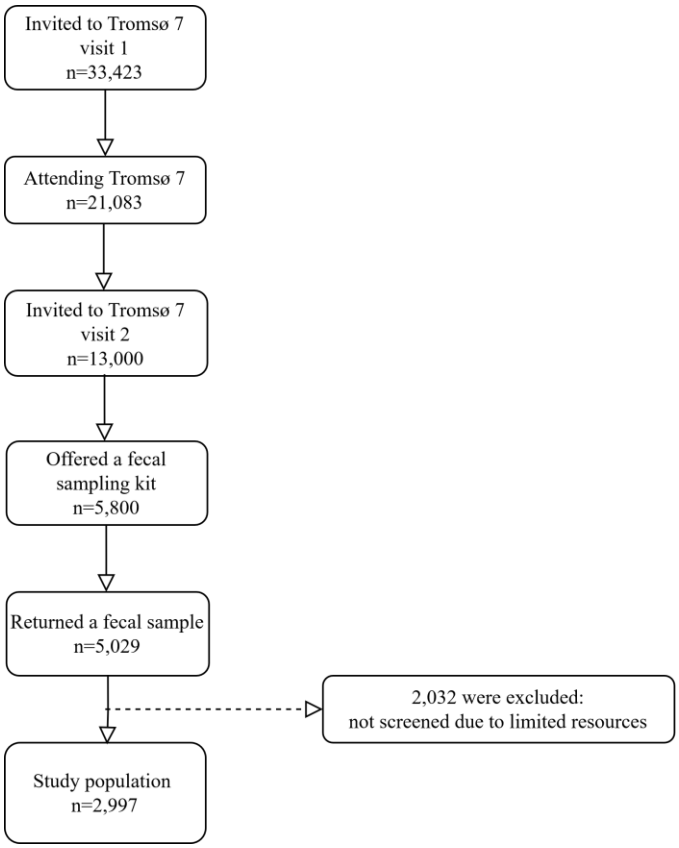


Figure 1. *Flow diagram of study population*

The study population consists of the participants who received results from the *K. pneumoniae* screening. 5800 fecal sampling kits were sent out to the participants. A total of 5029 participants sent fecal samples to the laboratory for screening. Due to limited resources, 2032 fecal samples were not screened for *K. pneumonia* in the laboratory. The final study population included 1375 men (46%) and 1622 women (54%), a total of 2997 participants. The mean age for the study population is 64 years. The participants have filled 40,643 prescriptions have been filled by the study population, in which men and women have filled 16,180 (40%) and 24,463 (60%) respectively.

3.3 ATC codes

All drugs with these ATC codes will be examined in this study: A02 (acid related disorders), A10 (diabetes), C10 (lipid modifying agents), J01, A07A, A09, P01A B01 (antibacterials for systemic use), H03 (thyroid drugs), M01 (anti-inflammatory and antirheumatic drugs), N02 (analgesics), N05 (psycholeptic) and N06 (psychoanaleptics). Psycholeptics comprise of antipsychotics, anxiolytics (used for treatment of disorders associated with anxiety) and

hypnotics and sedatives used. Psychoanaleptics comprise of antidepressant, psychostimulants (e.g. used for ADHD) and anti-dementia drugs.

3.4 Definition of *K. pneumoniae* carriage

Fecal samples were sent into the laboratory for screening of *K. pneumoniae* carriage. 200µl 85% glycerol was added to each ESwab and the samples were stored at -80°C. 100µl liquid from the thawed ESwab were directly plated onto Simmons citrate with inositol medium agar plates and incubated 48 hours at 37°C (25). Large, yellow, glossy colonies suspected of being Klebsiella spp. were identified using mass spectrometry (MALDI-TOF, Bruker Daltonics, Bremen, Germany). The participants were identified as *K. pneumoniae* carriers if one of the colonies on the agar plate were identified as *K. pneumoniae*.

3.5 Data preparation

We received two data files, one from NorPD and one from Tromsø 7. The dataset from NorPD received most of the attention as it was necessary to clean and prepare the data for further statistical analysis. We recoded the data to identify the unique drug forms such as tablet, injections and nasal sprays. This step made it possible to estimate a treatment length for a prescription dispensation (a detailed description of this step in 3.7.1 Examples of assuming a duration for a drug dispensation). The NorPD data was split into two files: a file for the source population and another for the study population. The source population differ from the study population by not having a date for fecal sample. Wherefore chose an arbitrary date to compare the two populations' drug use. We chose the 20th October 2015 as it is the 50^{th} percentile of the date fecal sample taken for the study population. Treatment episodes were constructed for both files. The file for study population had to be merged with the Tromsø 7 file to create a complete file with all the all the necessary variables from NorPD and Tromsø 7.

3.6 Variables

The raw dataset from NorPD consists of 26 variables. Despite the number of variables in this dataset, only a few variables will be central for us to achieve the aims of this study. The raw dataset from Tromsø 7 consists of 21 variables in which most of them will be considered as central variables for our study. All of the variables will be listed in Appendix. Some of these variables will be useful to create other new central variables.

3.6.1 Central variables

Patient's anonymized identification number is central as it identifies each participant throughout the data preparation and analysis. Date of dispensing and date of fecal sample taken could be used to calculate number of days between the dispensation date and fecal sample date. The new variable is used to exclude prescription dispensations that fall outside a set date interval. Amount of DDD dispensed is important as it will be used for the analysis for cumulative exposure. The variable that represents the results from the *K. pneumoniae* screening is also important as it is our depended variable in all the multivariable logistics regressions and cumulative change graph.

3.7 Constructing treatment episodes

Treatment episodes were constructed as they are crucial in drug-exposure and outcome association studies. However, a few steps must be considered in order to construct successful treatment episodes. Using different definitions could lead to potentially different conclusions even though the same dataset is used (26).

Firstly, the NorPD does not contain any details on the drug dosage regimen for each individual patient, which is important in order to estimate the length of a treatment. Drugs are used in a vast variety of ways and could therefore have different dosage regimens. As a result, the treatment episodes must be estimated on other information that the NorPD contains such as the DDD, date of prescription dispensed and number of packages/package size dispensed.

A simple approach to this problem is to assume that patients take 1 DDD of the prescribed drug daily (27,28). The WHO definition of the defined daily dose (DDD) is "the assumed average maintenance dose per day for a drug used for its main indication in adults" (29). Although the DDD seem to be the standard unit used in pharmacoepidemiologic studies, it still has its limitations. The study population might have a different dosage regimen for a specific drug because it is used for other indications, or their health status-related factors might affect the dosage regimen such as a reduced kidney function. Assuming that individuals take 1 DDD daily might lead to bias as it does not reflect the true dosage regimen for every individual.

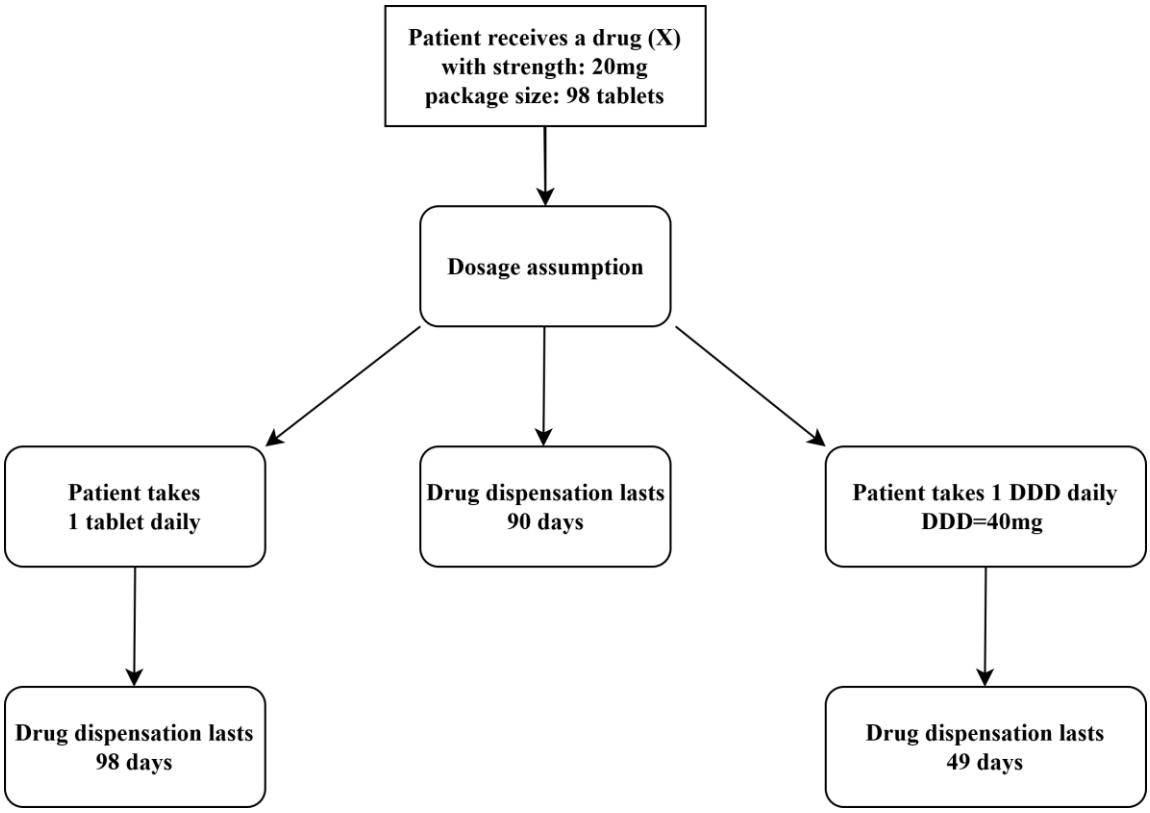


Figure 2. Representation of different drug exposure definitions and the following outcomes.

In this study a more detailed and individual-centered solution was chosen to capture the actual dosage regimen for each individual. Three possibilities were represented as seen in figure 2. The first possibility was to assume individuals took 1 unit daily e.g. 1 tablet daily. Drugs with the typical dosage regimen of 1 unit daily regardless of indication and health-related factors was assigned to this possibility such as statins (30). The second possibility was to assume that a drug dispensation lasted 90 days as it is the maximum allowed days of drug supplies to be dispensed from the Norwegian pharmacies under normal conditions (31). The third possibility was to assume that individuals took 1 DDD daily as previously mentioned. Figure 2 shows how the three possibilities could affect the duration of the drug dispensations. Felleskatalogen (FK) and Norsk Legemiddelhåndbok (NLH) was used as sources to decide and assume how long the treatments should last (32,33). FK is a Norwegian encyclopedia for every drug with marketing authorization in Norway and assures information about the typical dosage regimen for the different drugs. NLH is also an encyclopedia for drug and treatment options, and is well suited for the general practitioner in areas they are not specialized in.

3.7.1 Examples of assuming a duration for a drug dispensation

PPIs and statins are frequently used drugs as they cover 8,8% (22,887) and 13,9% (36,084) of the total 259,349 prescriptions dispensed. The most frequently used PPI and statin will be used as examples. The DDD for pantoprazole (A02BC02) is 40mg and the preferred dosage regimen is either 20mg or 40mg daily. The DDD for simvastatin (C10AA01) is 30mg and the preferred dosage regimen is 20-80mg daily. Simvastatin are available in different strengths, and can be taken as 1 tablet daily. In this scenario, individuals dispensing either pantoprazole or simvastatin, will be using 1 tablet daily regardless of dosage. Some drugs have a dosage regimen required to take several tablets daily, such as the antibiotic vancomycin (A07AA09). Individuals dispensing vancomycin 125mg capsules, will consume 4 capsules daily rather than 1 DDD which equals 2g. The dosage regimen for vancomycin is 125-500mg x 4 times daily. 500mg x 4 can be used when the infection is serious or complicated, however we are assuming that the case for serious and complicated infections are few.

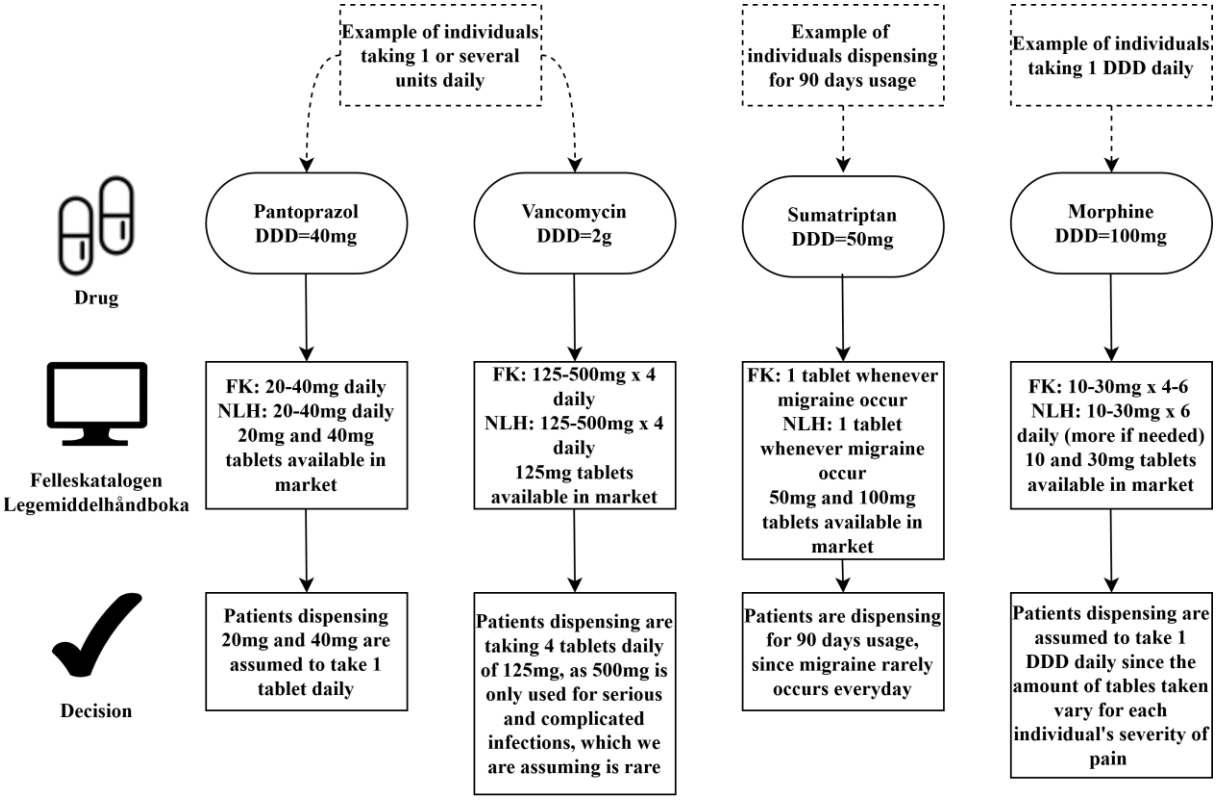


Figure 3. Represents the examples of assuming a duration for a drug dispensation

Some drugs are intermittently. Assuming a realistic treatment length for such drugs are complicated. Triptans are an example as they are used when symptoms of migraine occur. Sumatriptan (N02CC01) tablets have a DDD of 50mg which would equal one tablet. Assuming that individuals take one DDD or tablet daily would not be realistic as occurrence of migraine very rarely happen every day. In this scenario, any dispensations of triptans will last 90 days.

Assuming a treatment length for pain relievers face similar challenges as the dosage regimen can show considerable variation. The usual dosage regimen for morphine (N02AA01) tablets is 10-30mg per 4-6 hours daily. Since we can't assume how many tablets that are taken daily, it was decided that individuals that dispensed morphine took 1 DDD daily instead of how many tablets. The DDD for morphine tablets is 100mg.

The assumed duration for every prescription dispensation is in the Appendix.

Adherence is defined as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (34). A patient's adherence can vary depending on several patient-related factors, such as lack of understanding in terms of their disease, previous experience with other pharmacological therapies and lack of motivation. Physician-related factors can also affect the adherence, as prescribing complex drug regimens and failing to explain the needed information upon treatment start can reduce the adherence (35).

There are no ways to assure that a patient has 100% adherence to a drug dosage regimen provided by the physician. However, in this study, the importance of including adherence seems appropriate as it somehow should reflect the patient's actual drug use. For this reason, it might also make the results more reliable. The threshold of adherence was set to 80% as patients are generally considered adherent if they minimally accomplish this percentage.

Proportion of days covered (PDC) was chosen as an approach to measure adherence. In PDC, the adherence is calculated by the number of days covered by a prescription divided by

number of days in a period. Early medicine refills are also taken in consideration as people generally refill a couple of days and weeks before their medicine supplies are empty (carryover). This approach may benefit the goal of the study compared to other adherence measurements such as Medication Possession Rate (MPR) (36,37)

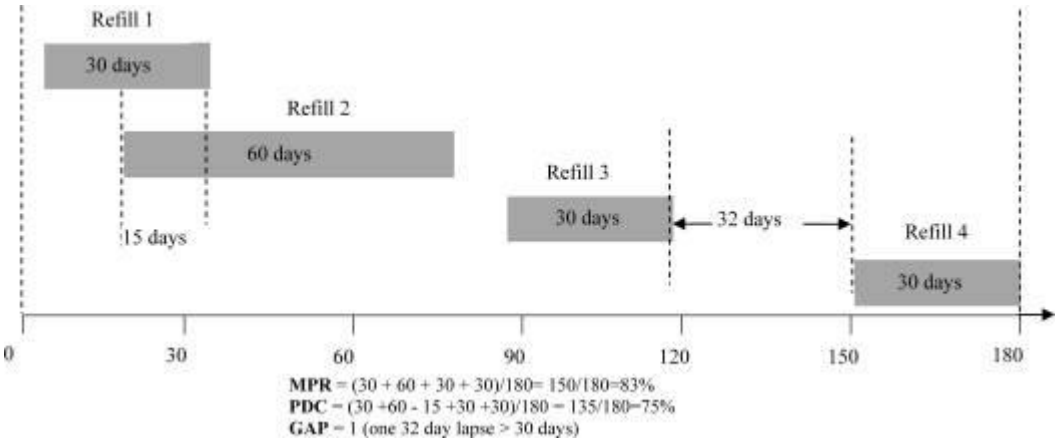


Figure 4. *An example of calculating MPR, PDC and GAP. Source: Zhu VJ et al. A Comparison of Data Driven-based Measures of Adherence to Oral Hypoglycemic Agents in Medicaid Patients* (37)

A patient's theoretical days coverage of received medicine supplies were calculated by multiplying the assumed duration of drug dispensation by 80% as they are considered adherent when reaching this threshold. Assuming a duration of a drug dispensation is explained in 4.7.1. By counting the number of days between two prescription refills of the same drug and taking in consideration the theoretical days coverage of the first refill, we can calculate how much medicine the patient has left before the refill. We can transfer the remaining medicine supplies from the first refill to the second refill and therefore calculate an end date for the treatment episode. If a patient tends to refill a couple of days earlier, the end date of their treatment episode will be calculated by the last refill's days coverage plus the remaining coverage from all their earlier refills.

The treatment episodes were constructed with an allowance of 14 days medicine-free gap between the supposed refill date and the actual refill date. For instance, if a patient refills later than two weeks after the supposed refill date, a new treatment episode is started. The start date of a treatment episode begins at the first prescription dispensation date and ends when the gap between the actual and supposed refill date differ by more than two weeks or if the patient doesn't refill anymore.

3.7.2 An example of a treatment episode construction

A patient was prescribed a drug (X) which has a typical dosage regimen of 1 tablet daily. They dispense the prescription in 1. July 2015 and receives 1 package which contains 100 tablets. The start date of the treatment episode is 1. January 2015 as it is their first dispensation of the drug. We assume that the patient should consume 1 tablet daily, but their adherence is 80% to the drug. Therefore, we could calculate how long the first dispensation would last, as dividing a package size of 100 tablets with 80% adherence would give us 125 days of medicinal coverage (100/0.8).

The first dispensation lasts till 6. May 2015 (supposed refill date) as the 125 days of the patient's medicinal coverage is empty. Since the patient could refill the prescription a couple of days in advance or behind the supposed refill date, this would give us three options.

The first option is if the patient refills a couple of days in advance to the supposed refill date, the remaining supplies (carryover) would be added to the next refill' end date. The patient refills in 1. May 2015 which is 5 days prior to the supposed refill date and receives the same package size containing 100 tablets. The new 100 tablets should last 125 days and in addition to the remaining carryover that should last 5 days, would give us 130 days of medicinal coverage. The 130 days should last till 13. September 2015.

The second and third option are if the patient refills a couple of days behind the supposed refill date. The same patient refills their prescription in 20. September 2015, which is 7 days behind the supposed refill date, 13. September 2015. Since it is within the two weeks medicine-free gap, we assume that the patient continues their treatment episode. However, if the patient refills after the two weeks medicine-free gap such as 30. September 2015, we assume that the patient discontinued the treatment episode and started on a new one. The treatment episode will therefore have a start date in 1. January 2015 and end in 13. September 2015.

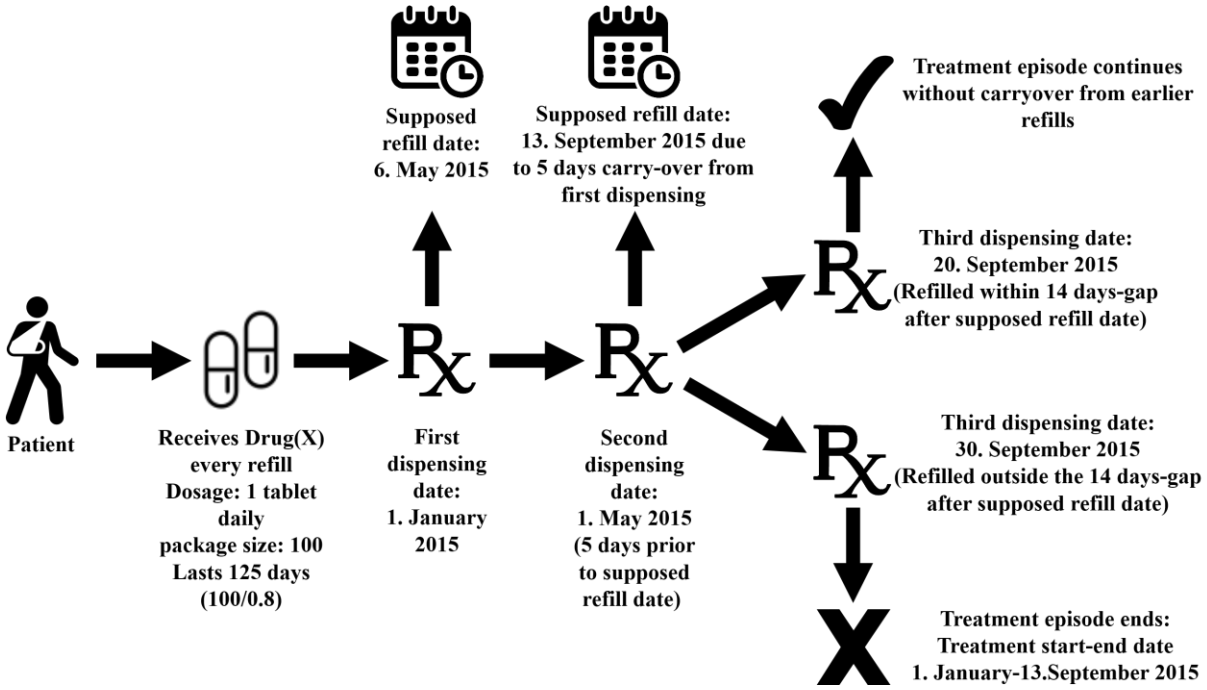


Figure 5. *Represents examples of the treatment episode definitions*

3.8 Study- and source population characteristics

A 12-month drug use before 20. October 2015 (chosen by 50th percentile of the date fecal sample taken for the study population) will be compared between the study and source population. Drug users are defined as having at least 1 prescription of a drug group dispensed in that 12-month period.

Clustering was done for the study population, as it is an important step in data analysis of unprepared and unknown relations in a data. Clustering is an organization of a collection of patterns into clusters based on similarity. Usually, patterns within a cluster are more similar to each other than patterns belonging to a different cluster (38). In other words, we want to divide the study population into clusters based on their drug use patterns. A 90 days interval before the fecal screening was set for the cluster analysis. All treatment episodes that ended before 90 days and started after fecal screening was not taken in consideration for the analysis.

K-means clustering was chosen as the approach to the clustering analysis. The are several advantages and disadvantages in choosing either K-means compared to other methods such as hierarchical clustering (38,39). K-means was primary chosen due to it requiring less computing power to operate the analysis compared to the hierarchical clustering in Stata®.

K-means clustering requires a beforehand chosen number of clusters (k), and therefore we chose 5-8 clusters based on an elbow-plot as a deciding factor. A tip from the Stata journal was followed to implement the elbow plot (40).

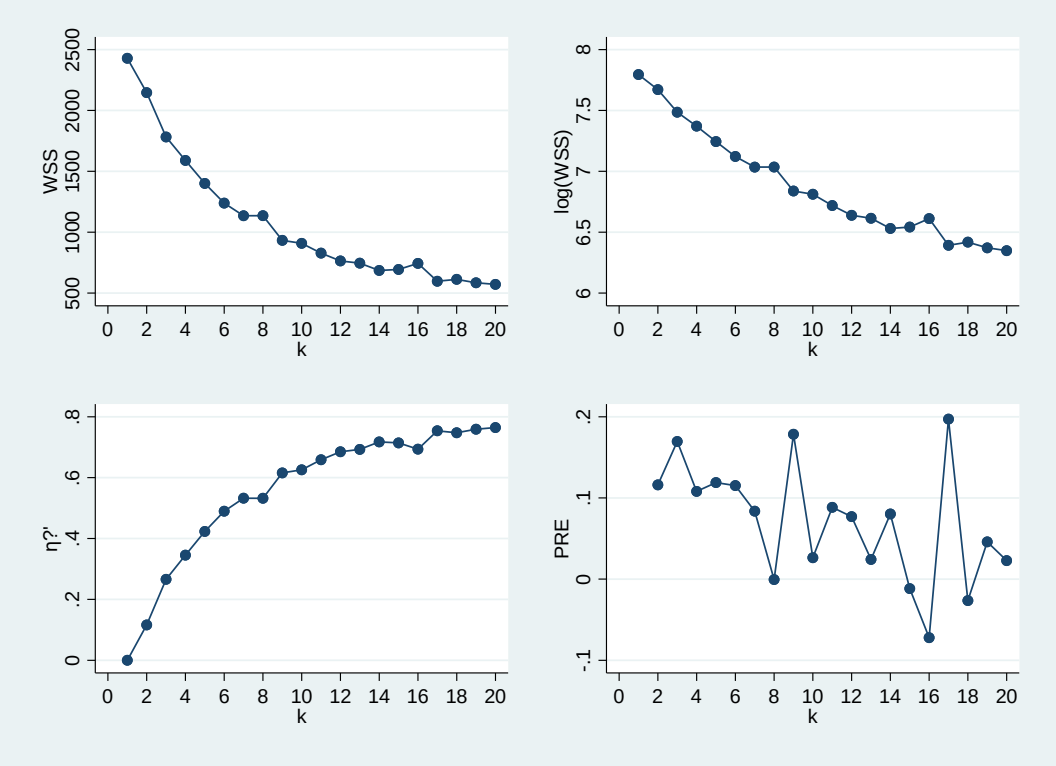


Figure 6. *WSS, log (WSS), η2, and PRE for all K cluster solutions*

The plots above indicate 7 clusters (k=7) to be optimal number of clusters in a k-means clustering. We are searching for a kink in the plots and according to the within sum of squares (WSS) and log(WSS), we can see a small kink when the k=7. The elbow plots do not represent a clear kink in their structure that we all can generally agree upon.

A Jaccard distance measure was used in k-means clustering as it works well with the binary variables used in the analysis. A participant was defined as being a drug user if they had a treatment episode within the 90 days interval. If they did not have a treatment episode, they were considered as non-drug user, therefore we have binary variables (drug user/ non-drug user).

Two radar plots and a table are used to represent the results from the k-means clustering.

3.9 Methods to study the associations between drug groups and *K. pneumoniae* carriage

We grouped all the drugs into groups according to the ATC level 2 before doing the analysis. For example, all proton pump-inhibitors (A02BC) and H2-antagonists (A02BA) were grouped into the drug group antacid (A02).

3.9.1 Studying if total exposure in DDD and daily dosage is associated with carriage

A time period of 180 days before the fecal screening was examined, as it seemed probable that the long-term carriage of *K. pneumoniae* would diminish as time goes by (41). All prescription dispensations outside the interval between 180 days before and till the fecal screening were removed. For antibiotics, the interval was set at 60 days before and till the fecal screening.

Two important actions were considered when calculating the total DDD accumulated in each treatment episode. The first one is made when the last dispensation for a treatment episode is dated within the interval, but its end date is after the fecal screening date. To avoid including the accumulated DDD after the fecal screening date, we had to do the following:

$$Fixed\ total\ DDD = \frac{total\ DDD}{\frac{total\ days}{difference\ between\ fecal\ screening\ date\ and\ start\ date}}$$

A simple explanation could for example be a patient that has accumulated 90 DDD in 180 days, however only the first 120 days were before the fecal screening date. Our point of interest is how much DDD the patient has accumulated before the fecal screening date. Putting this in the formula above would result in the patient accumulating 60 DDD.

The second consideration were relevant when the treatment episode started within the interval, but some of the dispensations were dated after the fecal screening date. We used the formula above with an adjustment in the "total days". In this situation it is the total days between first dispensation within the interval and first dispensation after the fecal screening date. For instance, a patient has accumulated 90 DDD and started 30 days before fecal screening date. Their next dispensation is 15 days after the fecal screening date, which results

in 45 total days from first dispensation within interval and first after the fecal screening date. Using the formula above we find out that the patient has accumulated 60 DDD.

Patient's total exposure in DDD for each drug group was calculated by summing the total DDD accumulated from the remaining treatment episodes within the time period.

A patient's daily dosage/intensity was calculated by dividing total exposure in DDD for a drug group with total days of medical coverage of that specific drug group.

A multivariable logistic regression will be implemented to study the association between total exposure of drug use and *K. pneumoniae* gastrointestinal carriage. Several variables will be adjusted for in the analysis, and the model is illustrated by a directed acyclic graph (DAG) explaining the relationship between the drug use (exposure), *K. pneumoniae* carriage (outcome) and other relevant covariates. See Appendix 4.

In order for our analysis to be valid, our models have to satisfy the assumptions of logistic regression. When the assumptions are not met, problems might arrive such as biased coefficient estimates or very large standard errors, and in the end lead to our analysis proving wrong statistical conclusions. Therefore, diagnostics are implemented to assess our models fit and occurring potential problems in our models.

3.9.2 Studying if time of drug use is associated with carriage

The end date of the last treatment episode of a drug group is the point of interest when studying time of drug use and its association with *K. pneumoniae* carriage. Only the past 12 months before the fecal screening date is investigated. This period differs from the 6 months restrictions used to study total exposure in DDD and daily dosage, since we want to consider if *K. pneumoniae* has the potential of long-term carriage. Treatment episodes lasting further than the fecal screening date is defined as current users and will be displayed as having the last time of drug use in month 0. The ATC codes A07, J01 and P01 will be aggregated to form the drug group antibiotics.

3.9.3 Studying if combinations of drug groups are associated with carriage

A drug user is defined as having a treatment episode of a specific drug in the past 6 months before the fecal sampling. All treatment episodes that started after fecal sampling or ended 180 days before fecal sampling were excluded. A Venn diagram will be used to illustrate the

combinations of the drug groups. Drug group antibiotics will be merged by the ATC codes J01 and P01.

3.10 Software

- Stata 16.1
- Microsoft office
- Mendeley as a reference manager program

All statistical analyses were done in Stata 16.1

3.11 Ethics

This study has received an approval from the Tromsø Study to use an already established dataset from Niclas Raffelsberger's phd-project (10). This dataset will be limited up to 20 variables to reduce the risk of backwards identification. An approval from the Norwegian Institute of Public Health (NIPH) to use and link the NorPD's dataset with the dataset of the Tromsø Study has also been received. The project for Raffelsberger has a REK approval (REK Nord: 14296) and the master student will be added to this approval as it falls within the overall aim of the approved project. The same applies to the already approved DPIA and data will be stored according to this DPIA.

4 Results

4.1 Study- and source population characteristics

4.1.1 Comparison between study and source population

Table 1. *A comparison of age, sex and number of drug users in the 12 months span before 20. October, between the study and source population. Drug users are defined as having at least 1 prescription dispensed in the period. The percentages show the proportion of users compared to the whole study population (n=2,997) and source population (n=21,083).*

	Study population (N=2,997)	Source population (N=21,083)
Age (in years)		
40-49	344 (11.48%)	6432 (30.51%)
50-59	438 (14.61%)	6035 (28.62%)
60-69	1295 (43.21%)	5179 (24.56%)
70-99	920 (30.70%)	3437 (16.30%)
Sex		
Male	1375 (45.88%)	11074 (52.53%)
Female	1622 (54.12%)	10009 (47.47%)
Drug users		
Antacida (A02)	654 (21.82%)	3794 (18.00%)
Antibiotics (A07)	1 (0.03%)	4 (0.02%)
Antidiabetics (A10)	168 (5.61%)	987 (4.68%)
Lipid-modifying drugs (C10)	846 (28.23%)	3852 (18.27%)
Thyroid drugs (H03)	279 (9.31%)	1522 (7.22%)
Antibiotics (J01)	1207 (40.27%)	7663 (36.35%)
Anti-inflammatory/antirheumatic drugs (M01)	1025 (34.20%)	7563 (35.87%
Analgesics (N02)	943 (31.46%)	6739 (31.96%)
Psycholeptics (N05)	628 (20.95%)	3987 (18.91%
Psychoanaleptics (N06)	171 (5.71%)	1376 (6.53%)
Antibiotics (P01)	82 (2.74%)	641 (3.04%)

Table 1 shows the difference between the study- and source population in age groups, sex and drug users. The study population consists of an older selection compared to the source population as the age groups 60-69 (43.21% vs 24.56%) and 70-99 (30.70 vs 16.30%) are bigger in favor of the study population. As for the drug use, the proportion of drug users are about equal in both populations except for the lipid-modifying drug users (28.23% vs 18.27%)

4.1.2 Drug use patterns of the study population

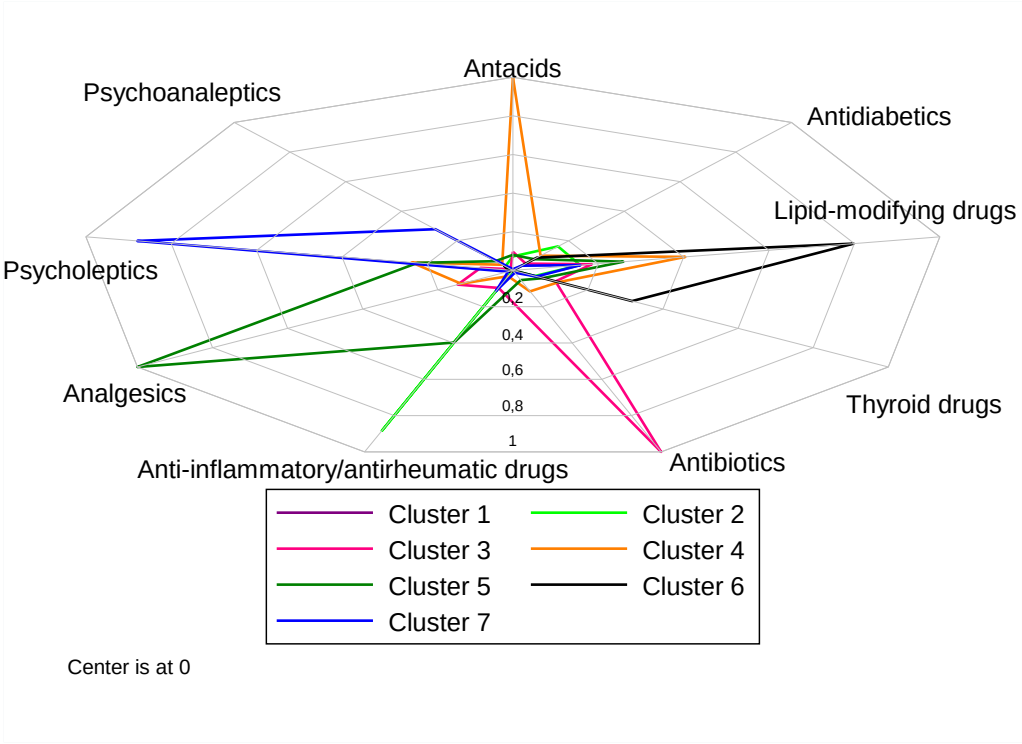


Figure 7a. *A radar plot representation of typical drug groups used by the seven different clusters.*

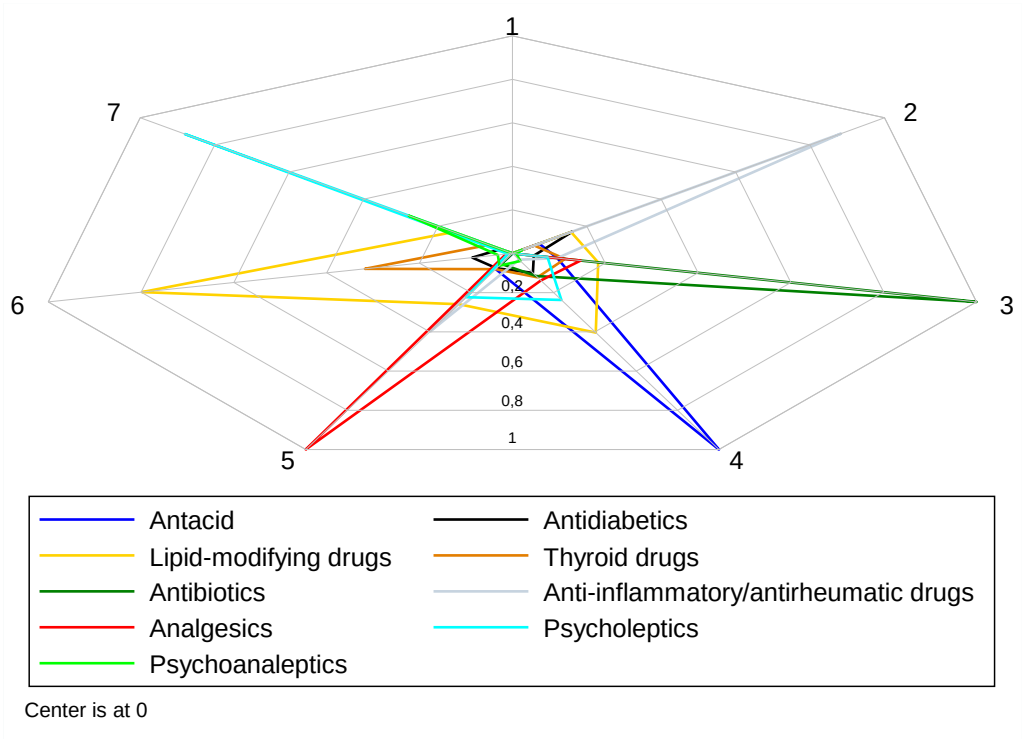


Figure 7b. *A radar plot with a different view on the typical drug groups used by the seven different clusters*

Figure 7a and b show different view of distinct drug use patterns that divide the seven different clusters. All clusters seem to have a specific characteristic that separates them from others, as most of them represent a majority of a drug group. Cluster 1 consists of only non-drug users. Cluster 2 consists mostly of only anti-inflammatory/antirheumatic drug users. Cluster 3 is heavily antibiotic represented as all participants from the cluster have used an antibiotic. Cluster 4 distinct from others by all participants being a user of antacid, whereas all participants from cluster 5 have used an analgesic. Cluster 6 have most of the lipid-modifying and thyroid drug using participants. Cluster 7 have most of psycholeptic and psychoanaleptic users.

Table 2. *A table representation of the typical drug groups used by the seven different clusters.*

	Cluster 1 (%)	Cluster 2 (%)	Cluster 3 (%)	Cluster 4 (%)	Cluster 5 (%)	Cluster 6 (%)	Cluster 7 (%)	Total (%)
Antacid	0	7.2	9.7	100	8.0	0	0.6	12.3
Antidiabetics	0	16.2	4.6	9.9	7.6	0,086	3.2	4.8
Lipid-modifying drugs	0	15.8	18.5	40.4	25.9	0,798	15.8	23.2
Thyroid drugs	0	5.9	11.3	12.2	8.0	0,318	6.3	8.9
Antibiotics	0	0	100	11.5	5.4	0	1.3	9.6
Anti-inflammatory/antirheumatic drugs	0	88.3	9.7	3.2	39.7	0,006	11.4	11.3
Analgesics	0	0	14.7	13.8	100	0,014	1.3	10.4
Psycholeptics	0	0	7.6	23.7	22.3	0,010	88.0	9.5
Psychoanaleptics	0	2.7	0.8	3.8	6.3	0,031	27.8	3.1

The colors are used to present how different each cluster's drug use mean is from the total mean. Green color: The specific cluster has the highest drug usage mean of a drug group, e.g. cluster 2 has the highest drug usage mean of antidiabetics. 16.2% of cluster 2 have used at least one antidiabetic within 90 days before fecal sample. Light green and orange color: Light green means that the cluster's drug usage mean is above the total mean and the opposite for orange. Red: The specific cluster has no users of a drug group. Yellow: The specific cluster has the same drug usage mean as the total mean, e.g. 3.1% of cluster 6 have used at least one psychoanaleptic which is also the total mean. Cluster 1 (n=1,333) Cluster 2 (n=222) Cluster 3 (n=238) Cluster 4 (n=312) Cluster 5 (n=224) Cluster 6 (510) Cluster 7 (158).

Table 2 represents the drug use mean from each cluster. A cluster with a mean of 1 implies that everyone from that specific cluster is a user of a drug group. A cluster with a drug use mean of 0 implies that none from that specific cluster is a user of a drug group. By looking at Table 2 and the second radar plot (Figure 7b), we can clearly see that Cluster 1 represent all the non-drug users. Cluster 3 separates itself from the other clusters by having all their participants being a drug user of an antibiotic. All participants from cluster 4 have at least been a drug user of an antacid.

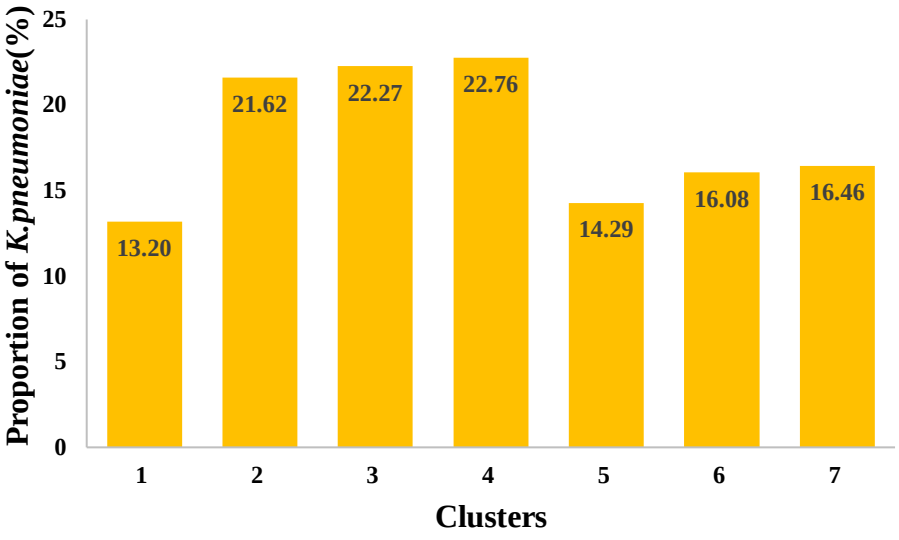
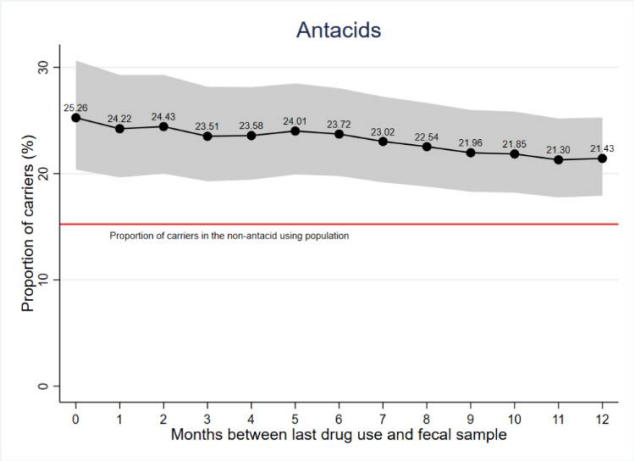


Figure 8. Proportion of carriers among the clusters

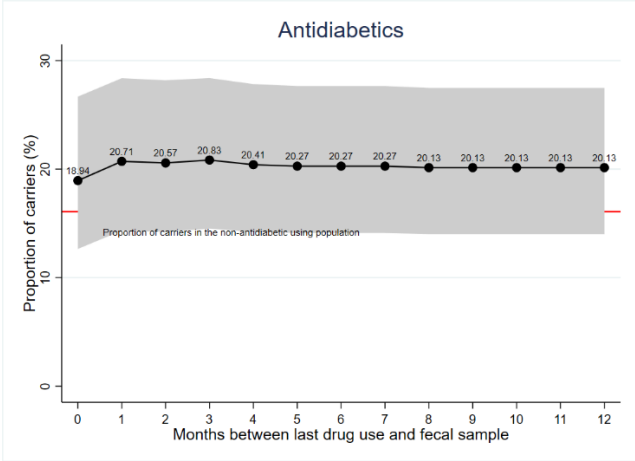
Figure 8 shows that cluster 1 which consists of only non-drug users have the lowest mean of *K. pneumoniae* carriers (13.20%). Cluster 4, where all participants have at least been a drug user of an antacid, have the highest mean of *K. pneumoniae* carriers (22.76%). Cluster 3 follows closely as the second highest mean of *K. pneumoniae* carriers (22.27%), which is

3 represented by all participants having at least dispensed one antibiotic in the past 90 days. Cluster 2 is not far away from the latter two clusters (21.62%) and is mostly represented by having the most drug users of anti-inflammatory/antirheumatic and antidiabetics (Table 2).

4.2 Association between time of drug use and *K. pneumoniae* carriage



a



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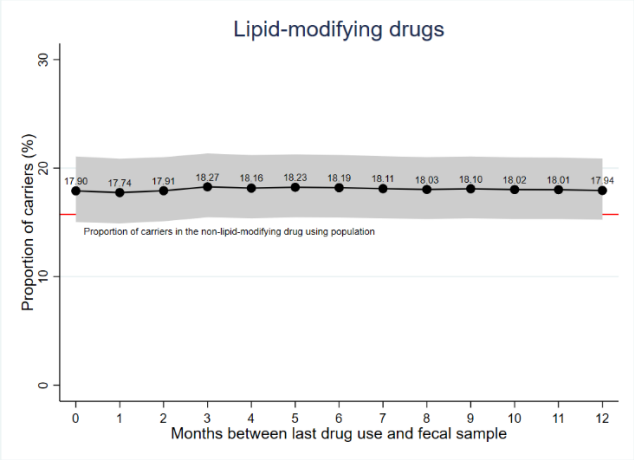

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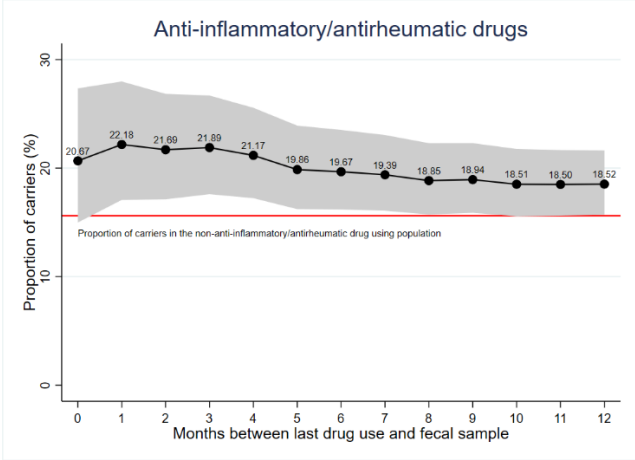

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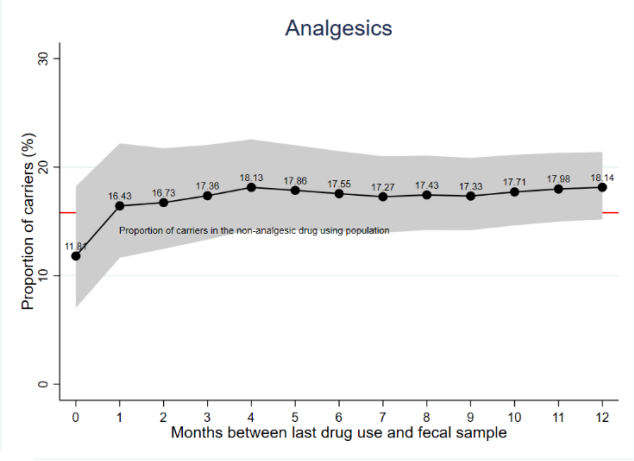

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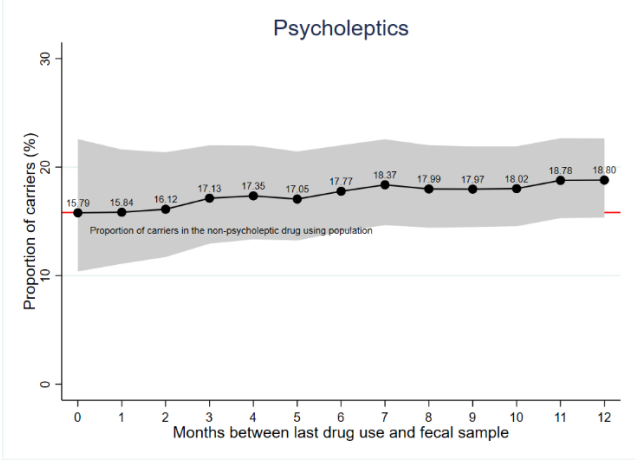

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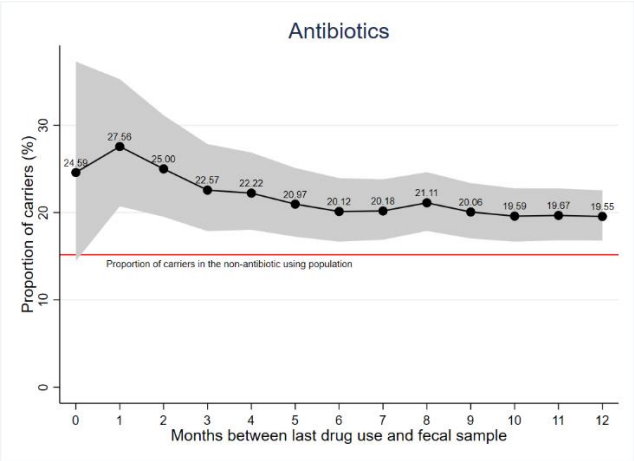

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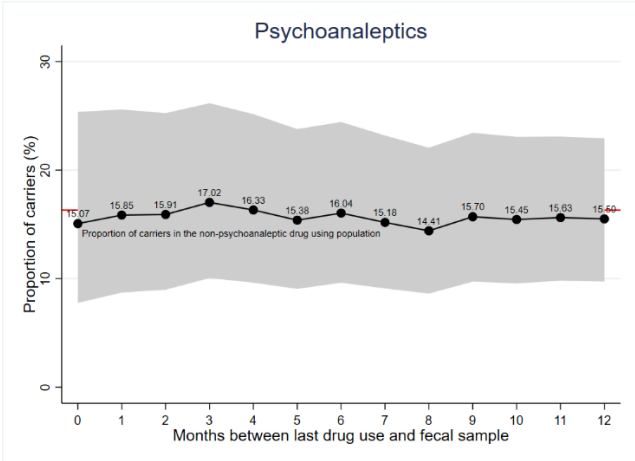

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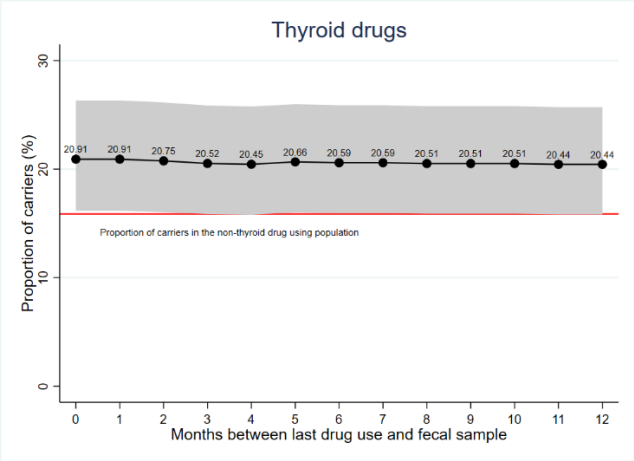

i

Figure 9a-i. *Cumulative change in the proportion of K. pneumoniae carriers among the participants who had used the nine different drug groups the past 1-12 months before the fecal sampling*
Month 0 is defined as being a current user. The grey area represents the 95 % CI. The time period at each specified month includes data from the preceding months. The red line indicates the prevalence of carriage in the non-drug using population for each drug group.

Looking at the graphs we see that for antidiabetics, lipid-modifying drugs analgesics, psycholeptics and psychoanaleptics drug the 95 % confidence interval overlaps the red line which indicates the prevalence of carriage in the non-drug using population (Figure 9 b,c,e,f,h).

Looking at the cumulative change in proportion of *K. pneumoniae* carriers associated with antacid (Figure 9a) use during the 12 months before fecal sampling, we find that the prevalence of *K. pneumoniae* carriage was the highest among current antacid users (25.26%) and decreases minimally throughout the 12 months with the lowest prevalence being around the last 11 to 12 months (21%). As for the non-antacid using population the prevalence of *K. pneumoniae* carriers was significantly lower (15.24%).

The thyroid drug using population's 95% confidence barely holds apart from the prevalence for *K. pneumoniae* for the non-thyroid using population (15.86%) except for the past 3-4 months and past 11-12 months (Figure 9i). The highest prevalence for carriage among the thyroid drug using population is among current users and users in the past month (20.91%). The prevalence for the thyroid drug using is barely decreasing and is at its lowest the past 11-12 months (20.44%).

Looking at the cumulative change graph for anti-inflammatory/antirheumatic drugs (Figure 9d), we can see that the highest prevalence of *K. pneumoniae* carriage belongs to the anti-inflammatory/antirheumatic drug using population the past month (22.18%) and decreases to its lowest in the last 10-12 months (18.5%). As for the non-anti-inflammatory/antirheumatic drug using population the prevalence for *K. pneumoniae* carriage is 15.61%. It is worthy to notice that the 95% confidence interval for the current users (month 0) crosses with the carriage prevalence of the non-anti-inflammatory/antirheumatic drug using population.

For the antibiotics use (Figure 9g), the highest prevalence of *K. pneumoniae* carriage is found the past month for the antibiotic using population (27.56%). The current users have a lower prevalence of carriage (24.59%), in addition to the 95% confidence interval also overlapping the red line. The prevalence of carriage decreases the past 5 months and then slowly decreases to around 20% afterwards. For the non-antibiotic using population the prevalence of *K. pneumoniae* carriage was 15.17%. The last use of an antibiotic was mostly drugs from the ATC code J01 as 992 participants used it last. 14 participants used P01 last, and none used A07 last.

4.3 Association between total exposure in DDD and *K. pneumoniae* carriage

Table 3. *A multivariable logistic regression analysis between the K. pneumoniae carriage and associated factors among the 2,997 participants in the Tromsø 7 study. The drug use exposure is defined in total DDD consumed the last 6 months before the fecal sampling and the last 2 months for antibiotics.*

	% (KP)	n (KP)	Denominator	AOR	95 % Cl	p-value
Drug use (in total DDD)						
Antacid (A02)	23.5	87	371	1.004	1.001-1.006	0.004
Antidiabetics (A10)	20.3	29	143	0.997	0.994-0.999	0.043
Lipid-modifying drugs (C10)	17.8	122	687	0.999	0.999-1.001	0.908
Thyroid drugs (H03)	20.2	53	263	1.001	0.997-1.004	0.752
Antibiotics (J01)	24.7	46	186	1.027	1.004-1.049	0.022
Anti-inflammatory/antirheumatic drugs (M01)	20.7	89	430	1.002	0.999-1.005	0.222
Analgesics (N02)	17.8	69	388	0.999	0.994-1.004	0.684
Psycholeptics (N05)	16.7	57	341	1.001	0.997-1.005	0.753
Psychoanaleptics (N06)	15.0	15	100	0.999	0.994-1.004	0.691
Antibiotics (P01)	40.0	2	5	0.829	0.453-1.516	0.542
Age	16.3	488	2997	1.016	1.005-1.028	0.005
Diabetes mellitus						
No	15.9	432	2711	1.000		
Yes	23.4	40	171	2.467	1.423-4.274	0.001
Bronchitis						
No	16.3	448	2756	1.000		
Yes	20.0	21	105	1.078	0.624-1.862	0.787
Hospitalization last 12 months						
No	15.9	423	2648	1.000		
Yes	18.6	65	349	1.009	0.730-1.396	0.954
Alcohol consumption frequency						
Never	16.5	43	261	1.000		
Monthly or less frequently	16.5	123	745	2.833	0.356-22.571	0.326
2-4 times a month to 2-3 times a week	16.8	299	1775	3.009	0.379-23.874	0.297
4 or more times a week	9.6	19	199	1.416	0.168-11.906	0.749
Alcohol units/occasion						
0	17.0	42	247	1.000		
1-4	16.3	416	2557	0.341	0.042-2.768	0.314
>4	14.1	20	142	0.260	0.029-2.269	0.223
6 alcohol units consumption frequency						
Never	15.9	279	1744	1.000		

Less frequently than monthly	17.2	163	946	1.204	0.942-1.539	0.138
Monthly	14.6	31	213	1.117	0.714-1.748	0.628
Weekly to a daily	13.4	9	67	1.228	0.553-2.728	0.614
Current daily smoking						
No	16.2	425	2616	1.000		
Yes	15.6	55	353	0.959	0.686-1.342	0.810
Crohn's disease/ulcerous colitis						
No	15.9	452	2833	1.00		
Yes	28.3	17	60	2.376	1.281-4.406	0.006

KP, K. pneumoniae. AOR, adjusted odds ratio. Cl, confidence interval.
AOR adjusted for age, diabetes mellitus, bronchitis, hospitalization past 12 months, alcohol consumption frequency, alcohol units/occasion, 6 alcohol units consumption frequency, current daily smoking, Crohn's disease/ulcerous colitis and the total DDD consumed for each drug group (ATC level 2) according to the NorPD (A02, A10, C10, H03, J01, M01, N02, N05, N06, P01).
The multivariable model contains 2,684 participants with complete information on all variables.
%(KP), n(KP) and denominator for drug use (in total DDD) is calculated by including only those who have used the specific drug group. %(KP) for age is the mean K. pneumoniae carriage among the 2,997 participants.

In the analysis adjusted for several variables it is shown that the number of total DDD consumed of antacid (A02), antidiabetics (A10) in the past 6 months and antibiotics (J01) in the past 2 months are associated with the gastrointestinal carriage of *K. pneumoniae*. Antacid use (A02) has an AOR of 1.004 and 95% Cl range of 1.001-1.006. Antidiabetics use (A10) has an AOR of 0.997 and 95% Cl range of 0.994-0.999. Antibiotics use (J01) has an AOR of 1.027 and 95% Cl range of 1.004-1.049. Furthermore, carriage was associated with increasement in age (AOR 1.016, 1.005-1.028), diabetes mellitus (AOR 2.467, 1.423-4.274) and Crohn's disease/ulcerous colitis (AOR 2.376, 1.281-4.406).

Model diagnostics were done and be found in appendix

4.4 Association between daily dosage and *K. pneumoniae* carriage

Table 4. *A multivariable logistic regression analysis between the K. pneumoniae carriage and associated factors among the 2,997 participants in the Tromsø 7 study. The drug use exposure is defined in total DDD consumed the last 6 months before the fecal sampling and the last 2 months for antibiotics divided by number of days.*

	% (KP)	n (KP)	Denominator	AOR	95 % Cl	p-value
Drug use (daily dosage/intensity)						
Antacid (A02)	23.5	87	371	1.321	0.974-1.792	0.073
Antidiabetics (A10)	20.3	29	143	1.032	0.699-1.525	0.873
Lipid-modifying drugs (C10)	17.8	122	687	0.962	0.792-1.168	0.695
Thyroid drugs (H03)	20.2	53	263	0.991	0.704-1.395	0.959
Antibiotics (J01)	24.7	46	186	1.949	1.301-2.920	0.001
Anti-inflammatory/antirheumatic drugs (M01)	20.7	89	430	1.284	0.980-1.682	0.070
Analgesics (N02)	17.8	69	388	1.104	0.725-1.680	0.645
Psycholeptics (N05)	16.7	57	341	0.932	0.608-1.429	0.748
Psychoanaleptics (N06)	15.0	15	100	0.898	0.491-1.640	0.725
Antibiotics (P01)	40.0	2	5	1.258	0.070-22.435	0.876
Age	16.3	488	2997	1.018	1.007-1.030	0.002
Diabetes mellitus						
No	15.9	432	2711	1.000		
Yes	23.4	40	171	1.579	0.978-2.550	0.062
Bronchitis						
No	16.3	448	2756	1.000		
Yes	20.0	21	105	1.083	0.628-1.869	0.774
Hospitalization last 12 months						
No	15.9	423	2648	1.000		
Yes	18.6	65	349	1.012	0.733-1.398	0.940
Alcohol consumption frequency						
Never	16.5	43	261	1.000		
Monthly or less frequently	16.5	123	745	2.749	0.344-21.970	0.340
2-4 times a month to 2-3 times a week	16.8	299	1775	2.917	0.367-23.210	0.312
4 or more times a week	9.6	19	199	1.375	0.163-11.597	0.770
Alcohol units/occasion						
0	17.0	42	247	1.000		
1-4	16.3	416	2557	0.352	0.043-2.868	0.329
>4	14.1	20	142	0.257	0.029-2.238	0.218
6 alcohol units consumption frequency						
Never	15.9	279	1744	1.000		
Less frequently than monthly	17.2	163	946	1.208	0.945-1.545	0.132

Monthly	14.6	31	213	1.112	0.710-1.741	0.643
Weekly to a daily	13.4	9	67	1.278	0.576-2.837	0.547
Current daily smoking						
No	16.2	425	2616	1.000		
Yes	15.6	55	353	0.970	0.695-1.355	0.860
Crohn's disease/ulcerous colitis						
No	15.9	452	2833	1.000		
Yes	28.3	17	60	2.355	1.271-4.363	0.006

KP, K. pneumoniae. AOR, adjusted odds ratio. Cl, confidence interval.
AOR adjusted for age, diabetes mellitus, bronchitis, hospitalization past 12 months, alcohol consumption frequency, alcohol units/occasion, 6 alcohol units consumption frequency, current daily smoking, Crohn's disease/ulcerous colitis and the total DDD consumed for each drug group (ATC level 2) according to the NorPD (A02, A10, C10, H03, J01, M01, N02, N05, N06, P01).
The multivariable model contains 2,684 participants with complete information on all variables.
%(KP), n(KP) and denominator for drug use (in total DDD) is calculated by including only those who have used the specific drug group. %(KP) for age is the mean K. pneumoniae carriage among the 2,997 participants.

In the analysis shown by table 5, only the amount of daily dosage of antibiotics (J01) among the drug groups was associated with gastrointestinal carriage of *K. pneumoniae* (AOR 1.949, 1.301-2.920). Increasement in age (AOR 1.018, 1.007-1.030) and Crohn's disease/ulcerous colitis (AOR 2.355, 1.271-4.363) was also associated with carriage.

4.5 Association between drug use combinations and *K. pneumoniae* carriage

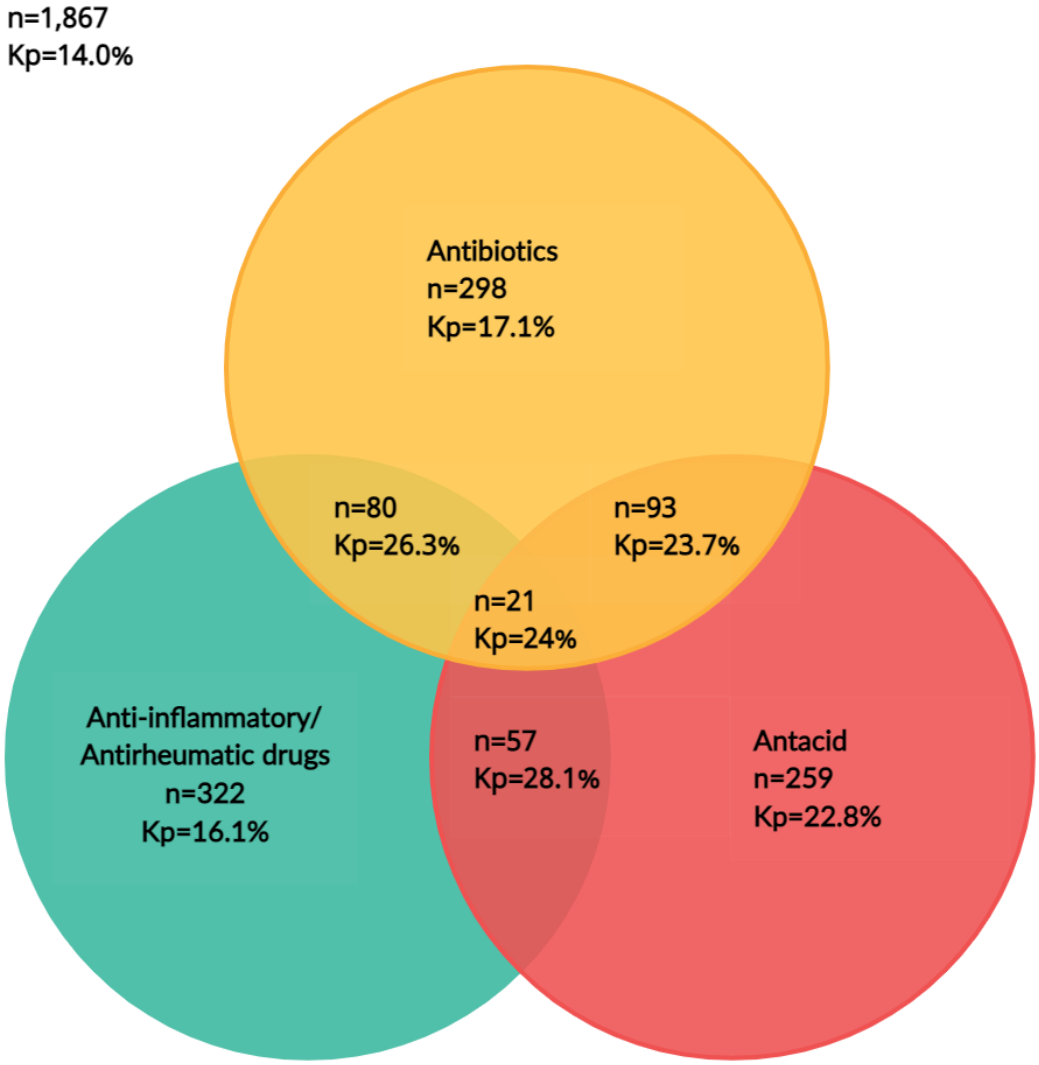

Figure 10. *Venn diagram of K. pneumoniae carriage prevalence among the users of antacid (A02), anti-inflammatory/antirheumatic drugs (M01) and antibiotics (J01, P01) in the past 6 months before fecal sampling among the 2,997 participants.*

The lowest prevalence of *K. pneumoniae* carriage were found among the 1,867 non-drug users of antacid, anti-inflammatory/antirheumatic and antibiotics (14.0%). The highest prevalence belongs to the 57 participants who used a combination of antacid and anti-inflammatory/antirheumatic drugs (28.1%). A combination of two drugs increased the overall prevalence of carriage compared to using a single drug, however when using a combination of all three drug groups, the prevalence could decrease. When going from a combination of

antacid and anti-inflammatory/antirheumatic to a combination of all three drugs, the prevalence decreased from 28.1% to 24.0%.

5 Discussion

The main findings from our study are that increased total exposure in DDD of antacid and antibiotics would result in higher odds of being a carrier. Increasing age, having diabetes mellitus and Crohn's disease/ulcerous colitis were also risk factors for being a carrier after being adjusted for. Whereas for daily dosage, increased DDD of antibiotics, increasing age and having Crohn's disease/ulcerous colitis were risk factors. Cumulative change graphs showed that the users of antacid, thyroid drug, anti-inflammatory/antirheumatic drug and antibiotics had an increased prevalence of carriage compared to the non-drug users throughout the past 12 months before fecal sample. I will now discuss the different results more in detail.

5.1 Clustering

Clustering is an effective method for partitioning a study population into subgroups based on drug use patterns. As a method, we used k-means clustering with seven predefined clusters. Based on the results, we found out that Cluster 1 which consisted of the non-drug users had the lowest *K. pneumoniae* carriage (13.20%). Cluster 2, 3 and 4 stood out from the rest as they had the highest prevalence of carriage. Cluster 4 had the highest proportion of antacid users and highest prevalence of carriage (22.76%). Cluster 3 had the second highest prevalence (22.27%) and were represented by the antibiotic users. Cluster 2 had the third highest prevalence (21.62%) and represented by mostly antidiabetic and anti-inflammatory/antirheumatic drug users (Table 2 for cluster characteristics and Figure 8 for *K. pneumoniae* carriage prevalence). These results were expected as the mentioned studies have shown that exactly antibiotics, anti-inflammatory/antirheumatic drug, antidiabetics and antacid influence the gut microbiome (13–19).

Cluster 5 had most of the analgesics users and had a prevalence of 14.29%.
Cluster 6 was represented by the users of lipid-modifying and thyroid drugs with a prevalence of 16.08%. Cluster 7 with a prevalence of 16.46% had the most users of psycholetics and psychoanaleptics. These clusters had a low prevalence of carriage although they didn't have the lowest such as the non-drug users. We expected that their prevalence would be equal or at least a bit higher due to drug use often being linked to other potential risk factors. For example, drugs are intended to treat some diseases that can possibly be a risk factor as they in

some way can alter the gut microbiome. Some participants can receive new prescriptions for drugs after being discharged from hospital which is an area with increased risk for carriage.

The cluster analysis results are only suggestions for drugs that might affect *K. pneumoniae* gastrointestinal carriage.

5.2 Time of drug use

The time of last drug use and gastrointestinal carriage of *K. pneumoniae* is an important aspect to investigate. We used cumulative change graphs to represent the change in *K. pneumoniae* carriers for each month before the fecal sampling (Figure 9). The drug-using population was compared to the non-drug using population in the graphs. Our findings revealed that antacid, thyroid, anti-inflammatory/antirheumatic drug and antibiotic users generally had a higher prevalence of carriage than non-drug users for almost the whole 12-month period (Figure 9a,d,g,i). This could imply that if these drugs have an effect on carriage, it will be long-lasting, lasting at least a year. It's possible that the effect is due to the drugs changing the microbiome in some way, or that the alterations in the microbiome are long-lasting. Compared to the clustering analysis and the other studies, the antidiabetic users did not have a significantly higher prevalence of *K. pneumoniae* carriage, as the 95% confidence interval intertwines the prevalence of the non-drug using population for every month. A cause of this might be due to a low number of antidiabetic users which can widen the confidence interval.

According to the cumulative change graphs, the thyroid drug using population had a higher prevalence of carriage than the non-drug using population in all the months apart from month 3,4, 11 and 12 before the fecal sampling (Figure 9i). The confidence interval barely crosses the prevalence of the non-drug using population in those months. This is a surprise as we had not hypothesized that thyroid drug use could affect the carriage. A majority of the thyroid drug users utilized levothyroxine (L-thyroxine), which is a synthetic T_4 hormone used to treat hypothyroidism as the body does not produce enough of this hormone by itself (42). In a retrospective study done by Brechmann et al. several factors were investigated to have an association with the development of small intestinal bacterial overgrowth (SIBO), which is defined as the presence of excessive bacteria in the small intestine, usually occupied by

bacteria that usually is not established there (43). L-thyroxine therapy was found to be the strongest contributor to the development of SIBO (OR 3.0).

In another study, Yao et al. investigated the association between the intestinal microbiome and L-thyroxine in subclinical hypothyroidism subjects. Patients were divided into two groups; patients receiving oral L-thyroxine and patients with no treatment. Patients receiving treatment were further divided in three groups based on their dose of L-thyroxine; low-, medium- and high dose. There was no difference in the abundance when comparing the treatment group with their control group. There was however discovered that the relative abundance of the genus *Odoribacter* and *Enteroccocus* increased according to the dosage increase in L-thyroxine. A 9-month follow up data was collected to divide the L-thyroxine treatment group into developing group and no develop group depending on whether the dose of L-thyroxine was increased during after 9 months. The relative abundance of the genus *Ruminococcus*, a dominant human gut microbiota, increased in the non-developed group compared to the developed group. The same goes for the other genera *Alistipes* and *Anaerotruncus* (44)

Treatment with L-thyroxine could alter the gut microbiome and gastrointestinal carriage of K. pneumoniae, but it's crucial to remember that the gut microbiome also influences thyroid function and thyroid hormone metabolism. It is difficult to assess whether a dysbiosis in the gut microbiome is the cause or the effect of thyroid dysfunction. The relationship between dysbiosis and thyroid dysfunction is complicated and can affect each other (45). Given these considerations, establishing a link between thyroid drug use and K. pneumoniae carriage is difficult.

Looking at the cumulative change graphs of antacid, thyroid, anti-inflammatory/antirheumatic drug and antibiotic, we can see the diminishing prevalence of carriage for every month between last time of drug use and fecal screening (Figure 9a,d,g,i). Depending on risk factors, the duration of a *K. pneumoniae* colonization in the gastrointestinal tract might range from months to years. After a significant single-center outbreak in Germany, Lübbert et al. investigated the long-term carriage of K. pneumoniae. They studied at the carrier prevalence one month, three months, six months, a year, and two years after *K. pneumoniae* was acquired. After one month, 26 of the 84 patients (31%) were decolonized. After three months,

14 of 34 patients (41%) were decolonized, and after six months, 17 of 26 patients (65%) were decolonized. After a one-year follow-up, 14 out of 19 (74%) of the patients tested negative for *K. pneumoniae*, and 5 out of 6 (83%) tested negative after two years. They also observed a patient with carrier status after nearly 40 months. According to their findings, carriage appears to decrease over time, with the greatest decline occurring within the first six months. A long-term carriage of >3 years is also possible (41). Feldman et al. also assessed the duration of carriage and discovered that the rate of *K. pneumoniae* positive patients was highest in the first 30 days after carriage was first detected, with 49 out of 66 patients testing positive (74%). After six months, the prevalence of carriage drops to <30% (46). The studies mentioned support our results in that the prevalence of carriage declines over time in the initial months, but the decline appears to be slower in our results, particularly among the thyroid drug users. The prevalence of carriage is 20.91% among current users and declined to 20.44% after a 12-month break between last thyroid drug use and fecal sampling.

Another interesting point is the cumulative graph of antibiotic usage (Figure 9g), which shows that current users have a low prevalence of carriage (24.59%) when compared to a one-month interval between previous antibiotic use and fecal sampling (27.56%). After a 12-month break, the prevalence dropped to 19.55%. The results could be explained by eradication and disruption of the microbiome, as well as the consequent effect of overgrowth promotion. Antibiotics are split into several classes, each with its own positive- or negative eradicating effects on the different bacteria. Sullivan and colleagues conducted a review based on clinical studies on the effects of antimicrobial drugs on human microflora published in the period of 1991-2001 (47). Vancomycin, linezolid, phenoxymethylpenicillin, ampicillin and amoxicillin showed an increase in number of *Klebsiella* species during treatment. Oppositely, trimethoprim/sulphamethoxazole strongly suppressed *Enterobacteriaceae* which includes *Klebsiella* species. Ruiz et al. studied the influence of antibiotic pressure on the multi-drug resistant *K. pneumoniae* colonization in critically ill patients. Adult patients admitted for more than 48 hours to an intensive care unit with no prior colonization of *K. pneumoniae* were included. They discovered a significant association between monthly colonization rate for *K. pneumoniae* and the use of cephalosporins and carbapenems in the previous month. There was no significant link between colonization and the use of the same antibiotics during the same month. They also found that patients that received antibiotics for more than 48 hours were colonized earlier than patients that did not receive this treatment. After 20 days in the

intensive care unit, there was a significant difference in the proportion of *K. pneumoniae* colonized between antibiotic-using and non-using patients. (48). The mentioned studies provide an insight on which antibiotics affect *K. pneumoniae* carrier status as well as colonization time following antibiotic usage. It should also be noted that the Ruiz et al. study only included individuals admitted to a hospital, which is a major risk factor for colonization, but hospitalization was not a requirement for inclusion in our analysis. This could theoretically lead to our participants expecting colonization to occur later than shown in our cumulative graph (Figure 9), as the incline from month 0 (24.59%) to month 1 (27.56%) could possibly be new emergences of *K. pneumoniae* after an antibiotic treatment. Furthermore, we did not study individual antibiotics and therefore can't confirm whether we can expect a lower or higher prevalence of carriage for current users as antibiotics can have different effects on *K. pneumoniae*.

5.3 Total drug exposure

Studying the association between total drug exposure/daily dosage and *K. pneumoniae* carriage is important as we can observe if a considerable amount of drug accumulation over a time period could increase the likelihood of being a carrier (Table 3). Accorded to our results when studying the association between total drug exposure and *K. pneumoniae* gastrointestinal carriage, the use of antacid and antibiotics (J01) increased the odds of a participant being a carrier. Antidiabetic use had a decreasing risk (AOR 0.997, 0.994-0.999), although caution should be taken, because when we used collinearity diagnostics to eliminate diabetes mellitus as a variable in our initial multivariable logistic regression, the p-value of antidiabetics shifted from significant to non-significant.

When analyzing drug usage as a continuous variable, the odds of being carrier increased by a certain percent for every DDD accumulated in the period adjusted for other potential risk factors. Although the adjusted odds ratio for drug use is modest in comparison to other studies, it is crucial to note that most studies utilize a categorical rather than a continuous variable to measure drug exposure (49,50). PPIs such as pantoprazole is a part of the antacid drug group and can in some cases be used as a long-term treatment of acid reflux and oesophagitis in a daily dosage of 20 mg and sometimes 40 mg in cases of relapses. Even if the adjusted odds ratio for antacid appears to be minimal (AOR 1.004), long-term treatment with pantoprazole, which requires the participant to consume 0.5 DDD daily, could result in a

substantially higher risk of K. pneumoniae carriage. A participant consuming 100 DDD of pantoprazole during the 6-month period would approximately increase their odd of being a carrier by 40%, as there is a 0.4% increase for every DDD consumed.

Increasing age, having diabetes mellitus and Crohn's disease/ulcerous colitis were also found being risk factors. Crohn's disease (CD) and ulcerous colitis are the two main types of inflammatory bowel disease (IBD). They cause chronic inflammation in the gastrointestinal tract which can cause symptoms such as abdominal pain, diarrhea and weight loss. IBD has shown to be related to dysbiosis as there have been a significant variation in bacteria diversity between healthy individuals and IBD patients. The relationship between IBD and dysbiosis is complex as it has been difficult to find clear evidence whether dysbiosis is a cause or a result of IBD (51–53). The typical bacteria diversity most associated with IBD is a reduced abundance of several types of commensal bacteria, particularly in *Firmicutes* and *Bacteroidetes,* and an increase in number of bacteria species belonging to *Enterobacteriaceae* (54,55). Accorded to our results, participants with IBD had an increased odd of being a *K. pneumoniae* carrier, but the causality is unknown because there is no clear evidence if being a carrier increases the likelihood of having IBD or vice versa. It's also possible that they'll both have an impact on each other.

The relationship between diabetes mellitus and gut microbiome changes has been studied frequently and the results have shown a different bacteria diversity pattern among the individuals with diabetes mellitus compared to individuals without. The studies suggest the alterations in the gut microbiome as a risk factor for development of diabetes mellitus (56–58)

The majority of the participants in our study population were in age groups of 60-69 (n=1,295) and 70-99 (n=920). An aging population have a significantly different bacteria diversity compared to a younger population. Factors such as diet, environment, genetics and pathological conditions contribute to the variation in the gut microbiome. Few gastrointestinal functions decline because of old age which could lead to an increased incidence of infections in the gut (59). Several studies have highlighted the changes in the gut microbiome due to age-related changes (60–63) . Hopkins et al. discovered an increased number of enterobacteria in the children's fecal sample compared to adults'. Odamaki et al. studied the gut microbiome changes in 367 healthy subjects from newborn to centenarian. They found out that infant- and

adult cluster had a significantly higher relative abundance of *Actinobacteria* and *Clostridia* whereas the elderly cluster had a significantly higher relative abundance of *Bacteroidetes, Betaproteobacteria* and *Deltaproteobacteria*. The studies did not take diet and lifestyle into account when studying the age-related changes in the gut microbiome. Our study accounts to some extent lifestyle as we have included smoking habits and alcohol consumptions, however a participant's dietary habits are not included.

5.4 Daily dosage

Examining if the daily dosage of the different drug groups can affect the gastrointestinal carriage is important as we can study if a high dosage can either increase or decrease the odds of being a carrier (Table 4). According to our results, only antibiotics (J01) out of the drug groups appears to influence the gastrointestinal carriage with an adjusted odds ratio of 1.949 (p=0.001). Meaning that using one additional DDD/day would increase their odds of being a carrier by 94%. Association between antibiotics and *K. pneumonia* carriage is well known and has been reported numerous times (46,50,64). This contrasts with our previous findings, which demonstrated that when total DDD exposure was taken into consideration, antacids, antidiabetics, and antibiotics were drug groups that could potentially alter gastrointestinal carriage. An explanation for this discrepancy could be because the use of antacids and antidiabetics affects gastrointestinal carriage over time, but the treatment intensity does not matter. A participant dispensing 100 DDD for a 100-day use period will have roughly the same chances of becoming a carrier as another dispensing 100 DDD for a 50-day use period.

Increasing age and the presence of Crohn's disease/ulcerous colitis are still considered risk factors, although having diabetes mellitus is not. The cause of the shift in diabetes mellitus as a risk factor is unknown.

5.5 Combination of drugs

We have looked at how a single drug could affect K. pneumoniae gastrointestinal carriage, but the use of two or more drugs is not uncommon and should be considered as they could dramatically increase or decrease the likelihood of being a carrier compared to using the drugs alone. Our Venn-diagram shows the prevalence of carriage for the utilization of three drug groups (Figure 10). According to the diagram we found an increasement of prevalence when two drug groups were used together, however the prevalence decreased when three drug

groups were used simultaneously. This was unexpected as we would assume three potential risk factors being used together would increase the prevalence even further compared to using two potential risk factors. Caution must also be taken as few users of all three drug groups can lead to randomness. Antibiotic, antacid and anti-inflammatory/antirheumatic drugs were chosen as they are considered most likely to be risk factors of *K. pneumoniae* gastrointestinal carriage according to our results. Our two multivariable logistic regressions do not see anti-inflammatory/antirheumatic drug usage as a risk factor, however it may be due to poor definitions of drug exposure and wrong subjective assumptions of drug treatment length (3.7.1 Examples of assuming a duration for a drug dispensation). It was also interesting to see the combination of antacid and anti-inflammatory/antirheumatic drugs as the former is used to treat ulcers that can be caused by the latter.

5.6 Discussion of method

The Tromsø 7 participants used a wide range of unique drugs for varying conditions, this made it very hard to do an individual assessment of daily dosage. We chose to assume that participants either used 1 tablet daily, 1 DDD daily or dispensed for 90 days which is the maximum allowed days of supplies to be dispensed in Norwegian pharmacies. Each of these subjective daily dosage assumptions made, could vary from person to person, if it is better to assume that a participant consumes 1 DDD on a daily basis. A study by T. Romppainen et. Supports this idea by showing that the dosage assumption of 1 tablet should be preferred over the dosage assumption of 1 DDD per day, as the DDD drug exposure definition would under- or overestimate the duration of statin prescriptions (30).

Treatment episodes play an important role in the investigation of drug utilization related outcomes such as prevalence and incidence (65,66). Patients rarely refill their prescription on the exact same day as the last use of their previous dispensing. They usually refill earlier (overlap between two dispensed prescriptions) or later (gap between two dispensed prescriptions). To account for these variations, researchers can allow a certain number of days (gap) between two dispensed prescriptions. These gap lengths can vary in days and sometimes be disregarded by the researcher. Determining the gap length should be based on the nature of the treatment. Duration of the treatment, different diseases and the following symptoms varies vastly and can be divided into short time, intermittent, chronic and episodic drug use. Short-term medications such as antibiotics should have an allowance of a few days,

whereas for intermittent, chronic and episodic therapies, the gap length could be less strict with a few weeks allowance (67). Due to the multiple considerations when deciding the gap length, we chose to use 14 days as an accepted gap for every drug, although an alternative decision would probably be to have a short gap length of a few days for antibiotics and a longer gap length for the other drug classes such as opioids, antacid and antidiabetics. This can lead to consequences such as treatment episode durations being increased, which in turn translate to over- or underestimating the exposure (drug use) has on outcome (carriage) (67).

The database gives complete and anonymous information on the patient, prescriber, medicine (i.e. exposure) and mortality incidence (i.e. outcome). Another strength is that pharmacy records are considered more complete than medical records, as only the prescriptions dispensed in pharmacies are entered into the NorPD database. This means that the primary non-compliance will be eliminated and therefore improve the validity of the data, whereas in medical records the agreement between prescribing and patient usage is to some extent unknown.

The prescription data also eliminate the potential recall bias that occur from survey data. The database is complete as all the Norwegian pharmacies are required to send their electronic data on all the prescriptions dispensed.

Oppositely, a disadvantage of the database is that it doesn't include the information on the drugs dispensed in hospital stays or nursing homes, which therefore could result in a underestimation of the total drug usage in the population (68).

The study population dispensed 144 different drugs before and after fecal sampling. When studying the last 12 months drug usage past the fecal sampling to see if there was a link between last use of a drug and *K. pneumoniae* carriage, the study population dispensed 129 unique drugs. As for the association between total DDD, daily dosage and *K. pneumoniae* carriage, the study population dispensed 118 unique drugs the past 6 months before fecal sampling. Due to the enormous number of different drugs dispensed, determining whether each individual drug has any effect on gastrointestinal carriage would be a very difficult and time-consuming operation. The number of users for each individual drug would also be an important factor on the results, as few users can lead to the results being less reliable. By

classifying all drugs into ATC code level 2 groupings we would have an increased possibility of robust results.

A disadvantage of this approach is that we can't distinguish in which way the exact drug/drug group might affect the gastrointestinal carriage because the ATC code level 2 groupings represent multiple drugs/drug groups rather than just one. Analgesics (N02) consist of the three drug groups; opioids (N02A), other analgesics and antipyretics (N02B) and antimigraine agents (N02C). An increase of *K. pneumoniae* carriage by analgesics use (N02) indicates that the use of at least one of the three drug groups promotes the carriage. However, we don't know if the other two drug groups have the same, opposite, or no effect on the carriage.

Gathering the drugs into ATC code level 3 groupings was also an opportunity, however the work would be much more complicated, and the number of drug users would also be a big factor.

5.7 Strengths and limitations

The strengths of this study are as follows:

1. Large scale of data on participation, exposure (prescriptions) and outcome (prevalence of *K. pneumoniae* carriage). The data collected in this study is among one of the biggest compared to other studies researching on risk factors for *K. pneumoniae* carriage. The Tromsø Study is also Norway's most comprehensive population study.
2. Good quality of data on both registers from NorPD and Tromsø Study, including important variables that are considered relevant on the demographic characteristics and the drug utilization. NorPD is a great and well-established register as they receive information on every drug dispensation from all Norwegian pharmacies.
3. Our approach on creating treatment episodes and having different assumptions on dosage regimen based on drug strength and formulation makes it more realistic and the results more reliable.
4. This is the first study to investigate how multiple characteristics of drug use, such as the last time a drug was used, total exposure in DDD, and daily dosage, can alter K. pneumoniae gastrointestinal carriage.

While limitations are:

1. Constructing treatment episodes are important to assess the relationship between drug exposure and outcome. They are however complex as several parameters must be decided upon and definitions must be made which are crucial for the final results. There are no straight forward answers to what is the right assumptions for these calculations
2. NorPD is our most important and reliable drug-based register, and we have access to variables to determine how a participant uses their drug, but they are not perfect in the sense that the daily dosage is not available. A variable with daily dosage for each individual dispensation would reflect a participant's supposedly true intake of drugs. Another limitation is the lack of information on drugs dispensed in the hospitals. Hospitalized participants receiving drugs from the hospitals would not be recorded to the database and therefore cause an underestimation of drug usage.
3. We made several assumptions on the dosage regimen for each drug dispensed in pharmacies which is a strength but can also be weakness as the assumptions are made subjectively based on the available information from drug encyclopedias. Other researchers can have a different opinion on whether we should assume a participant taking 1 tablet daily or 1 DDD daily.
4. Our study is limited to the most crucial variables we believe are important in order to achieve our study aims and to keep the participants anonymized. Our analysis have adjusted for several risk factors, but there is a possibility that other crucial risk factors exist without our knowing. Traveling overseas and diet are two potential risk factors as we often have a need for probiotics due to new surroundings/food disrupting and altering our gut microbiome.
5. We assumed that participants are 80% adherent to their prescribed dosage as we can't assure that a participant takes all their drugs as prescribed by the doctor. A minimum threshold of 80% is also required to be considered adherent. Although an assumption of 80% adherence is appropriate, it should be based on the types of drugs the participant takes. Antibiotics are most the of time used as a short-term treatment in which the participants would probably be closer to fully adherent. Long-term treatments such as with statins, participants can sometimes forget to take their dosage and therefore 80% adherence can be assumed to be reasonable. As a result, the duration of antibiotic treatment is likely overestimated. However the impact of this on the analyses will be

minimal as adding a few days would not alter severely and in return interpret the results the wrong way.

6. Only adults aged ≥40 years old were invited to Tromsø 7. This is a limitation as it would be interesting to see if the results also apply to those younger than 40. Looking back to our findings suggesting increasing age to be a risk factor for *K. pneumoniae* carriage, we would expect younger adult having a lower prevalence of carriage.
7. Due to limited resources, almost half of the fecal samples were not screened. More samples would have further increased the precision of our results.
8. We divided the drug use into groups based on ATC code level 2 (e.g. A02, A10, J01). Assessing the drug use based on these groupings can limit our potential information extracted from the data available, as we can't tell if any individual drug can increase the odds of a participant being a carrier. Dividing the drugs into ATC code level 3 would be a better solution as drugs in the same group usually have the same mechanisms of action, but this was not feasible because it would be more complicated and the number of users for each drug would also be worrying.
9. We only looked at the prevalence for *K. pneumoniae* carriage for those who used a combination of the three drug groups; antacid, anti-inflammatory/antirheumatic drugs and antibiotic.

5.8 Future work

1. Our approaches in the treatment episode construction can further be tested by comparing the accuracy and reliability of the results when using another approach on the same dataset. We assumed that participants followed their given dosage 80% of the time for each drug dispensation, but we believe that assigning an individual adherence rate based on the drug dispensation would yield a more reliable result. A different approach on how to decide the dosage regimen should be tested. We assumed participants took either 1 tablet, 1 DDD or dispensed for 3 months use based on the drug strength and formulation.
2. Our study was limited to the use of drug groups based on ATC code level 2. This works well as an indicator on which drug groups that could potentially affect the gastrointestinal carriage. For future works, it would be better to focus on the exact drugs or drug groupings based on ATC code level 3.
3. Our study was limited to adults aged ≥40 years. It would be recommended to conduct research on also those aged under 40 to see if the results differ.
4. A combination of drug use and how that affect the gastrointestinal carriage should be looked upon in future works. We have seen from our findings that older people are more at risk for gastrointestinal carriage. They are also exposed to polypharmacy which is often defined as the use of 5 or more medications (69).

6 Conclusion

Klebsiella pneumoniae colonizes the gastrointestinal tract depending on a number of risk factors. Antibiotic use has long been recognized as a risk factor, whereas the research on non-antibiotic drugs have been few. This study aimed to investigate which drug groups and combination could alter the gastrointestinal carriage of *K. pneumoniae*. Our findings suggest antacid, thyroid drugs, anti-inflammatory/antirheumatic drugs and antibiotics as potential risk factors. Increasing age, having diabetes mellitus and Crohn's disease/ulcerous colitis are also suggested as risk factors. Using a combination of two drugs increased the prevalence of carriage whereas a combination of three decreased when focusing on antacid, anti-inflammatory/antirheumatic drugs and antibiotic. Future studies should be carried out to confirm whether these drug groups are risk factors and in the long-term, research which exact drug poses an increased risk compared to others.

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Appendixes

Appendix 1: Stata coding

//Data preparation

```
use "C:\T7 OG RESEPTREGISTERET\Legemidler og bærerskap\RReg_korr_20191101 - Kopi.dta"

// Exporting to excel-file in order to create new variables which could be used to group all
the drugs into unique drugs formulas such as tablets, capsules, mixture.
keep VARENR VAREPAKNINGSTR VAREPAKNINGENHET VAREPAKNINGSTYRKE ATCKODE VARENAVN
duplicates drop
export excel using "C:\T7 OG RESEPTREGISTERET\Legemidler og bærerskap\Excel fil for Rreg.xls",
firstrow(variables)
import excel using "C:\T7 OG RESEPTREGISTERET\Legemidler og bærerskap\Excel fil for Rreg.xls",
firstrow // opening new stata file and importing it in there
save "C:\T7 OG RESEPTREGISTERET\Legemidler og bærerskap\Rreg_new_variables.dta"
merge m:1 VARENR using "C:\T7 OG RESEPTREGISTERET\Legemidler og
bærerskap\Rreg_new_variables.dta"
recode PLASTER INJEKSJON NESESPRAY MIKSTUR STIKKEPILLE REKVÆSKE MUNNSPRAY DOSEPOSER
TABLETTKAPSEL (.=0)
drop _merge

// Cleaning and converting a string variable to numeric
replace AtcKodeDDDEnhet = "mcg" if AtcKodeDDDEnhet =="mg"
replace AtcKodeDDDEnhet = "mg" if AtcKodeDDDEnhet=="g"
replace VAREPAKNINGSTR="98" if VAREPAKNINGSTR=="98x1"
replace VAREPAKNINGSTR="100" if VAREPAKNINGSTR=="100x1"
replace VAREPAKNINGSTR="104" if VAREPAKNINGSTR=="104x1"
replace VAREPAKNINGSTR="10" if VAREPAKNINGSTR=="10x1"
replace VAREPAKNINGSTR="100" if VAREPAKNINGSTR=="10x10"
replace VAREPAKNINGSTR="20" if VAREPAKNINGSTR=="10x2"
replace VAREPAKNINGSTR="14" if VAREPAKNINGSTR=="14x1"
replace VAREPAKNINGSTR="18" if VAREPAKNINGSTR=="18x1"
replace VAREPAKNINGSTR="20" if VAREPAKNINGSTR=="20x1"
replace VAREPAKNINGSTR="200" if VAREPAKNINGSTR=="20x10"
replace VAREPAKNINGSTR="24" if VAREPAKNINGSTR=="24x1"
replace VAREPAKNINGSTR="28" if VAREPAKNINGSTR=="28x1"
replace VAREPAKNINGSTR="1" if VAREPAKNINGSTR=="2x0,5"
replace VAREPAKNINGSTR="56" if VAREPAKNINGSTR=="2x28"
replace VAREPAKNINGSTR="100" if VAREPAKNINGSTR=="2x50"
replace VAREPAKNINGSTR="180" if VAREPAKNINGSTR=="2x90"
replace VAREPAKNINGSTR="196" if VAREPAKNINGSTR=="2x98"
replace VAREPAKNINGSTR="30" if VAREPAKNINGSTR=="30x1"
replace VAREPAKNINGSTR="32" if VAREPAKNINGSTR=="32x1"
replace VAREPAKNINGSTR="3" if VAREPAKNINGSTR=="3x1"
replace VAREPAKNINGSTR="4.5" if VAREPAKNINGSTR=="3x1,5"
replace VAREPAKNINGSTR="30" if VAREPAKNINGSTR=="3x10"
replace VAREPAKNINGSTR="6" if VAREPAKNINGSTR=="3x2x1"
replace VAREPAKNINGSTR="9" if VAREPAKNINGSTR=="3x3"
replace VAREPAKNINGSTR="90" if VAREPAKNINGSTR=="3x30"
replace VAREPAKNINGSTR="40" if VAREPAKNINGSTR=="40x1"
replace VAREPAKNINGSTR="49" if VAREPAKNINGSTR=="49x1"
replace VAREPAKNINGSTR="2" if VAREPAKNINGSTR=="4x0,5"
replace VAREPAKNINGSTR="8" if VAREPAKNINGSTR=="4x2"
replace VAREPAKNINGSTR="80" if VAREPAKNINGSTR=="4x20"
replace VAREPAKNINGSTR="112" if VAREPAKNINGSTR=="4x28"
replace VAREPAKNINGSTR="50" if VAREPAKNINGSTR=="50x1"
replace VAREPAKNINGSTR="250" if VAREPAKNINGSTR=="50x5"
replace VAREPAKNINGSTR="56" if VAREPAKNINGSTR=="56x1"
replace VAREPAKNINGSTR="5" if VAREPAKNINGSTR=="5x1"
replace VAREPAKNINGSTR="7.5" if VAREPAKNINGSTR=="5x1,5"
replace VAREPAKNINGSTR="10" if VAREPAKNINGSTR=="5x2"
replace VAREPAKNINGSTR="12.5" if VAREPAKNINGSTR=="5x2,5"
replace VAREPAKNINGSTR="15" if VAREPAKNINGSTR=="5x3"
replace VAREPAKNINGSTR="60" if VAREPAKNINGSTR=="60x1"
replace VAREPAKNINGSTR="3" if VAREPAKNINGSTR=="6x0,5"
replace VAREPAKNINGSTR="6" if VAREPAKNINGSTR=="6x1"
replace VAREPAKNINGSTR="90" if VAREPAKNINGSTR=="90x1"
replace VAREPAKNINGSTR="96" if VAREPAKNINGSTR=="96x1"
destring VAREPAKNINGSTR, replace
```

```
// Fixing the old variable which was multiplied by 1000 beforehand
generate ORDINASJONANTALLPAKNINGER2 = ORDINASJONANTALLPAKNINGER/1000
replace ORDINASJONANTALLPAKNINGER = ORDINASJONANTALLPAKNINGER2
drop ORDINASJONANTALLPAKNINGER2
generate ORDINASJONANTALLDDD2 = ORDINASJONANTALLDDD/1000
replace ORDINASJONANTALLDDD = ORDINASJONANTALLDDD2
drop ORDINASJONANTALLDDD2
```

//Assumption of treatment length for every drug dispensation

```
// Creating an assumed treatment length of a drug dispensation for tablets. Currently it is
assumed the dosage regimen is 1 tablet daily.
gen FAKETREATMENTLENGTH=VAREPAKNINGSTR*ORDINASJONANTALLPAKNINGER
gen TREATMENTLENGTH=0
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if TABLETTKAPSEL==1
gsort ATCKODE - TABLETTKAPSEL PasientLopeNr_PDB2720 UTLEVERINGSDATO

// replacing TREATMENTLENGTH for each ATC if the dosage regimen > 1 tablet daily or taken as
needed.

// A02A Antacid
replace TREATMENTLENGTH=90 if ATCKODE=="A02AD01" // Novaluzid. Taken as needed
replace TREATMENTLENGTH=90 if ATCKODE=="A02AH" // Natriumhydrogenkarbonat. Taken as needed

// A02B Drugs for peptic ulcer and gastro-esophageal reflux disease (GERD)
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="A02BA02" // Ranitidin. Unique dosage
regimen depended on indication
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="A02BA03" // Famotidin. Unique dosage
regimen depended on indication
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/3 if ATCKODE=="A02BB01" // Misoprostol. 2-4
tablets daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/3 if strpos(ATCKODE,"A02BX") // Sukralfat,
Alginsyre. 2-4 tablets daily

// A07A Intestinal anti-infectives
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/4 if ATCKODE=="A07AA09" // Vancomycin. 125mg x 4.

// A10B Blood glucose lowering drugs, excl. insulins
replace TREATMENTLENGTH=90 if ATCKODE=="A10BA02" // Metformin.
500-1000mgx2-3. Unique dosage depended on severity/kidney
replace TREATMENTLENGTH=90 if ATCKODE=="A10BB01" // Glibenklamid. 1,75-10,5mg. Unique dosage
depended on blood glucose level
replace TREATMENTLENGTH=90 if ATCKODE=="A10BB07" // Glipizid. 2,5mg-15mg. Unique dosage
depended on blood glucose level
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="A10BD07" // Metformin and
sitagliptin. 2 times daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="A10BD08" // Metformin and
vildagliptin. 2 times daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="A10BD11" // Metformin and
linagliptin. 2 times daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/3 if ATCKODE=="A10BF01" // Akarbose.50-100mgx3.
replace TREATMENTLENGTH=90 if ATCKODE=="A10BH02" // Vildagliptin. Unique dosage depended on
combination with other antidiabetics
replace TREATMENTLENGTH=90 if ATCKODE=="A10BX02" // Repaglinid. Unique dosage depended on how
many main meals

// C10 Lipid modifying agents
replace TREATMENTLENGTH=(VAREPAKNINGSTR/4)*ORDINASJONANTALLPAKNINGER if ATCKODE=="C10" //
Hypocol (rød gjæret ris). 2x2.
replace TREATMENTLENGTH=90 if ATCKODE=="C10AC04" // Colesevelam. 4-7 tablets daily. Dosage
depended on combination/mono treatment.
replace TREATMENTLENGTH=90 if ATCKODE=="C10AX06" // Omega-3-triglyserider + annet. 2-6
capsules daily.

// H03 Thyroid therapy
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="H03AA02" // Liotyroninnatrium.
Maintenance dose 2-3 tablets.
replace TREATMENTLENGTH=90 if ATCKODE=="H03AA05" // Levotyroksin(t4)and liotyronin (t3).
Unique dosage.
```

```
// J01 Anti-infectives for systemic use
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01AA02" // Doksysyklin. Unique
dosage depended on indication and severity
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01AA04" // Lymesyklin. Unique dosage
depended on indication
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01AA07" // Tetrasyklin. Unique
dosage depended on indication and severity
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01CA04" // Amoksicillin. Unique
dosage depended on indication and severity
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/3 if ATCKODE=="J01CA08" // Pivmecillinam. 200-
400mgx3
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/4 if ATCKODE=="J01CE02" // Fenoksymetylpenicillin.
660-1gx4
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01CF01" // Dikloksacillin. 3-4
tablets daily. Unique dosage depended on severity. Can increase to 6 tablets daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01CF02" // Kloksacillin. Outdated
Ekvacillin tablets
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01DB01" // Cefaleksin. 2-4 tablets
daily. Unique dosage depended on indication and severity
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01DC02" // Cefuroksim. Unknown
dosage
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01EA01" // Trimetoprim. Unique
dosage depended on indication
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01EE01" // Sulfametoksazol and
trimetoprim. Unique dosage depended on indication
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01FA01" // Erytromycin. DDD of
1000mg.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01FA09" // Klaritromycin. Unique
dosage depended on indication and severity. Normal DDD is 500mg.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01FA10" // Azitromycin. Unique
dosage depended on indication.
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/4 if ATCKODE=="J01FF01" // Klindamycin. Unique
dosage depended on severity. Normal dosage is 150mgx4. Dosage is 300mgx4 in severe cases
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="J01MA01" // Ofloksacin. Unique
dosage depended on indication and severity. Usual dosage is 200mgx2.
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="J01MA02" // Ciprofloksacin. 2
tablets daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01MA12" // Levofloksacin. Unique
dosage depended on indication and severity.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01MA14" // Moksifloksacin.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01XC01" // Fusidin tabletter.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01XE01" // Nitrofurantoin. Unique
dosage depended on severity
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="J01XX05" // Metenamin. 2 times
daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="J01XX08" // Linezolid. 2 times
daily

// M01A Anti-inflammatory and antirheumatic products, non-steroids
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="M01AB01" // Indometacin. 25-50mgx2-3.
Maximum 150mg daily.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="M01AB05" // Diklofenak. Unique dosage
depended on indication.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="M01AB55" // Diklofenak og
misoprostol. 1 tablet 2-3 times daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="M01AC01" // Piroksikam. Usually 1
tablet daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="M01AC06" // Meloksikam. 1 tablet
daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/4 if ATCKODE=="M01AE01" // Ibuprofen. 3-4 tablets
daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="M01AE01" &
VAREPAKNINGSTYRKE=="800mg" // Ibuprofen. Differ between depot(2tbl daily) and normal tablet
(3-4tbl daily)
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="M01AE02" // Naproksen. 2 tablets
daily.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="M01AE03" // Ketoprofen.
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="M01AE03" & VAREPAKNINGSTYRKE=="200mg"
// Ketoprofen. Those who dispense 200mg use 1 tablet daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="M01AE52" // Naproksen and
esomeprazol. 1-2 tablets daily
replace TREATMENTLENGTH=90 if ATCKODE=="M01AG02" // Tolfenamsyre. Used for migraines
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="M01AH01" // Celekoksib. 1-2 tablets
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daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="M01AH05" // Etorikoksib. 1 tablet
daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/3 if ATCKODE=="M01AX" // Glukosamin and
kondroitin. 3 capsules daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="M01AX01" // Nabumeton.
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/3 if ATCKODE=="M01AX05" &
VAREPAKNINGSTYRKE=="400mg" // Glukosamin. Depended on strength. Those who dispense 400mg use 3
times daily, while 625mg use 1-2 times daily.
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="M01AX05" & VAREPAKNINGSTYRKE=="625mg"
// Glukosamin. Reduce dosage to 1 tablet for when symptom relief
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="M01CB03" // Auranofin. 2 tablets
daily

// N02A Opioids
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AA01" // Morfin.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AA05" // Oksykodon.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AA55" // Oksykodon and nalokson.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AB01" // Ketobemidon.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AB03" // Fentanyl.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AE01" // Buprenorfin.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AJ06" // Kodein and paracetamol.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AJ07" // Acetylsalisylsyre,
koffein and kodein.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AJ13" // Tramadol and paracetamol.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AX02" // Tramadol.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AX06" // Tapentadol.

// N02B Other analgesics and antipyretics
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02BA01" // Acetylsalisylsyre.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02BB51" // Fenazon og koffein
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/3 if ATCKODE=="N02BE01" // Paracetamol. Usually
1x3.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02BE51" // Paracetamol, combination.
+ koffein.

// N02C Antimigraine preparations.
replace TREATMENTLENGTH=90 if ATCKODE=="N02CA72" // Ergotamin.
replace TREATMENTLENGTH=90 if ATCKODE=="N02CC01" // Sumatriptan.
replace TREATMENTLENGTH=90 if ATCKODE=="N02CC02" // Naratriptan.
replace TREATMENTLENGTH=90 if ATCKODE=="N02CC03" // Zolmitriptan.
replace TREATMENTLENGTH=90 if ATCKODE=="N02CC04" // Rizatriptan.
replace TREATMENTLENGTH=90 if ATCKODE=="N02CC05" // Almotriptan.
replace TREATMENTLENGTH=90 if ATCKODE=="N02CC06" // Eletriptan.
replace TREATMENTLENGTH=90 if ATCKODE=="N02CC07" // Frovatriptan.
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="N02CX02" // Klonidin. 2 tablets
daily

// N05A Antipsychotics
replace TREATMENTLENGTH=90 if ATCKODE=="N05AA01" // Klorpromazin. 25-600mg/daily
replace TREATMENTLENGTH=90 if ATCKODE=="N05AA02" // Levomepromazin.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05AB03" // Perfenazin. 8-64mg/daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05AB04" // Proklorperazin. 10-
125mg/daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05AD01" // Haloperidol. 2-12mg/daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05AF03" // Klorprotiksen. 25-
600mg/daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05AF05" // Zuklopentiksol. 10-
60mg/daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05AH02" // Klozapin. 25-600mg/daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="N05AH03" // Olanzapin. 5-20mg/døgn. 1
tablet daily.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05AH04" // Kvetiapin. 300-
800mg/daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05AN01" // Litium. FK: Maintanence
dose is 4-10 depot tablets of 42mg or 2-5 of 83mg.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05AX08" // Risperidon.
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="N05AX12" // Aripiprazol. NLH: 10-
30mg/døgn. 1 tablet daily.

// N05B Anxiolytics
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05BA01" // Diazepam.
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replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05BA04" // Oksazepam..
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/3 if ATCKODE=="N05BA12" // Alprazolam. NLH:
tablets take 3-4. depot tablets take 1-2 ganger. None participant use depot.
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="N05BB01" // Hydroksyzin. FK: 10-
30mgx2-3 or 35-50mgx2
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05BE01" // Buspiron. Maintanence
dose 15-30mg

// N05C Hypnotics and sedatives
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05CD02" // Nitrazepam. NLH: 2,5-5mg
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05CD03" // Flunitrazepam. NHL: 0,5-
1mg
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="N05CF01" // Zopiklon. NLH: 3,75-
7,5mg. Elders use 1/2 tablet of 7,5mg
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="N05CF02" // Zolpidem. NLH: 10mg.
Elders use 1 tablet of 5mg
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="N05CH01" // Melatonin. 2mg/daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05CM02" // Heminevrin.

// N06A Antidepressants
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AA04" // Klomipramin. FK:
Maintenance dose 50-100mg for depression
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AA05" // Opipramol.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AA06" // Trimipramin. FK:
maintenance dose 100-200mg for depression
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AA09" // Amitriptylin. Individual
maintenance dose
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AA10" // Nortriptylin.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AA12" // Doksepin. NLH: initially
50mg. can increase to max 200-250mg.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AB03" // Fluoksetin. FK:
recommended start dose 20mg/daily. Can increase up to 60mg/daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AB04" // Citalopram. FK:
recommended 20mg/daily. Can increase to 40mg.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AB05" // Paroksetin. Dosage
depended on indication. FK: 20mg daily for depression
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AB06" // Sertralin. FK: 50mg
daily. Can increase after response
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AB08" // Fluvoksamin. FK:
Recommended dose 100mg
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="N06AB10" // Escitalopram. FK: Normal
dose 10mg. Can increase to 20mg. 20mg tablets exist in market
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="N06AG02" // Moklobemid. FK:
Recommended 300mgx2. Can increase to 600mgx2
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AX03" // Mianserin. FK: Initially
30mg daily. Can increase. Effective dose is usually 30-90mg
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AX11" // Mirtazapin. FK: Start
dose 15-30mg/daily. Effective dose is between 15-45mg/daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="N06AX12" // Bupropion. FK: Start dose
150mgx1. Can increase to 300mgx1
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AX16" // Venlafaksin. FK: Start
dose 75mgx1. Can increase depended on indication
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AX18" // Reboksetin. FK:
Recommended dose 4mgx2. Can increase to 10mg daily. Max 12mg daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AX21" // Duloksetin. FK: Start and
maintenance dose is 60mgx1. Can increase
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="N06AX26" // Vortioksetin. FK: Start
and recommended dose is 10mgx1. Can increase and decrease although they take 1 tablet anyway

// N06B Psychostimulants, agents used for ADHD and nootropics
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06BA02" // Deksamfetamin. FK:
Recommended start dose 5mgx1-2. Can increase
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06BA04" // Metylfenidat. Depot is 1
tablet daily and normal tablets are 2 daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06BA07" // Modafinil. FK:
Recommended dose is 100mgx2. Can increase to 100mgx4
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="N06BA09" // Atomoksetin. FK:
Maintenance dose is 80-100mg/daily. Takes 1 tablet daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="N06BA12" // Lisdekamfetamin. FK:
Start dose 30mgx1. Max 70mgx1
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06BC01" // Koffein.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06BX03" // Piracetam.
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// N06D Anti-dementia drugs
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="N06DA02" // Donepezil. FK: Start dose
5mgx1. Can increase to 10mgx1
replace TREATMENTLENGTH=FAKETREATMENTLENGTH/2 if ATCKODE=="N06DA03" // Rivastigmin. FK: 2
tablets daily
replace TREATMENTLENGTH=FAKETREATMENTLENGTH if ATCKODE=="N06DX01" // Memantin. FK: 1 tablet
daily

// P01A Agents against amoebiasis and other protozoal diseases
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="P01AB01" // Metronidazol. FK: Unique
dosages depended on indication

// Creating an assumed treatment length of a drug dispensation for patches
replace TREATMENTLENGTH=15*ORDINASJONANTALLPAKNINGER if ATCKODE=="N02AB03" & PLASTER==1 //
Fentanyl. FK and NLH: Switch patches after 3 days. All packages have 5 patches.
replace TREATMENTLENGTH=28*ORDINASJONANTALLPAKNINGER if ATCKODE=="N02AE01" & PLASTER==1 //
Buprenorfin. FK and NLH: Switch patches after 7 days. All packages dispensed have 4 patches.
replace TREATMENTLENGTH=30*ORDINASJONANTALLPAKNINGER if ATCKODE=="N06DA03" & PLASTER==1 //
Rivastigmin. FK og NLH: Switch patches everyday. All packages have 30 patches.

// Creating an assumed treatment length of a drug dispensation for injections
replace TREATMENTLENGTH=5*ORDINASJONANTALLPAKNINGER if ATCKODE=="A02BC02" & INJEKSJON==1 //
Pantoprazol powder for injection. FK: 40mg (1 vial) per day. All packages have 5 vials.
replace TREATMENTLENGTH=90 if ATCKODE=="A10AB01" & INJEKSJON==1 // Fast-acting insulin
(human).
replace TREATMENTLENGTH=90 if ATCKODE=="A10AB04" & INJEKSJON==1 // Fast-acting insulin lispro.
replace TREATMENTLENGTH=90 if ATCKODE=="A10AB05" & INJEKSJON==1 // Fast-acting insulin aspart.
replace TREATMENTLENGTH=90 if ATCKODE=="A10AB06" & INJEKSJON==1 // Fast-acting insulin
glulisin.
replace TREATMENTLENGTH=90 if ATCKODE=="A10AC01" & INJEKSJON==1 // Intermediate-acting insulin
(human).
replace TREATMENTLENGTH=90 if ATCKODE=="A10AD05" & INJEKSJON==1 // Combination
intermediate/long-acting with with fas-acting insulin aspart.
replace TREATMENTLENGTH=90 if ATCKODE=="A10AE04" & INJEKSJON==1 // Long-acting insulin
glargin.
replace TREATMENTLENGTH=90 if ATCKODE=="A10AE05" & INJEKSJON==1 // Long-acting insulin
detemir.
replace TREATMENTLENGTH=90 if ATCKODE=="A10AE06" & INJEKSJON==1 // Long-acting insulin
degludec.
replace TREATMENTLENGTH=28*ORDINASJONANTALLPAKNINGER if ATCKODE=="A10BJ01" & INJEKSJON==1 &
VAREPAKNINGSTR==4 // Eksenatid. Bydureon. FK og NLH: 2mg depotinjection 1 weekly. Already 4
injections inside.
replace TREATMENTLENGTH=30*ORDINASJONANTALLPAKNINGER if ATCKODE=="A10BJ01" & INJEKSJON==1 &
VAREPAKNINGSTR==60 // Eksenatid. Byetta. FK og NLH: 5 or 10 microgram injections 2 times
daily. 6 doses in 1 package.
replace TREATMENTLENGTH= ORDINASJONANTALLDDD if ATCKODE=="A10BJ02" & INJEKSJON==1 //
Liraglutid. Victoza. FH og NLH: Start with 0,6mg. Increase to 1,2mg and 1,8mg if needed.
replace TREATMENTLENGTH=ORDINASJONANTALLPAKNINGER*4*7 if ATCKODE=="A10BJ05" & INJEKSJON==1 //
Dulaglutid. FK og NLH: 0,75mg or 1,5mg weekly. Alle packages have 4 injections.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="C10AX13" & INJEKSJON==1 //
Evolokumab. FK og NLH: Recommended 140mg every other week or 420mg monthly
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01CF02" & INJEKSJON==1 //
Kloksacillin. FK og NLH: Varied dosage
replace TREATMENTLENGTH=90 if ATCKODE=="J01DD01" & INJEKSJON==1 // Cefotaksim.
replace TREATMENTLENGTH=ORDINASJONANTALLPAKNINGER if ATCKODE=="M01AB05" & INJEKSJON==1 //
Diklofenak. FK: 75mg up to 150mg if no effect
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AA01" & INJEKSJON==1 // Morfin. FK
og NLH: Varied dosage
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AA05" & INJEKSJON==1 // Oksykodon.
FK: Varied dosage
replace TREATMENTLENGTH=90 if ATCKODE=="N02CC01" & INJEKSJON==1 // Sumatriptan. FK og NLH:
Normal dosage 6mg. Can increase to 12mg.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05AD01" & INJEKSJON==1 //
Haloperidol. FK og NLH: Varied dosage.
replace TREATMENTLENGTH=ORDINASJONANTALLPAKNINGER*14 if ATCKODE=="N05AH03" & INJEKSJON==1 //
Olanzapin. FK og NLH: 210mg every 2. Week.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05BA01" & INJEKSJON==1 // Diazepam.
FK: initially 10mg. Can be used several times in a day
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05CD08" & INJEKSJON==1 // Midazolam.
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// Creating an assumed treatment length of a drug dispensation for nasal spray
replace TREATMENTLENGTH=90 if ATCKODE=="N02CC01" & NESESPRAY==1 // Sumatriptan.
replace TREATMENTLENGTH=90 if ATCKODE=="N02CC03" & NESESPRAY==1 // Zolmitriptan.

// Creating an assumed treatment length of a drug dispensation for liquid solutions
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="A02BX02" & MIKSTUR==1 // Sukralfat.
FK: Dosage depended on indication
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="A02BX13" & MIKSTUR==1 // Alginsyre.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01CA04" & MIKSTUR==1 //
Amoksicillin.
replace TREATMENTLENGTH=ORDINASJONANTALLPAKNINGER*VAREPAKNINGSTR/10 if ATCKODE=="J01CE02" &
MIKSTUR==1 & VAREPAKNINGSTYRKE=="250mg/ml" // Fenoksymetylpenicillin. FK: Drops have dosage
10ml/daily
replace TREATMENTLENGTH=ORDINASJONANTALLPAKNINGER*VAREPAKNINGSTR/40 if ATCKODE=="J01CE02" &
MIKSTUR==1 & VAREPAKNINGSTYRKE=="50mg/ml" // Fenoksymetylpenicillin. FK: Mixture have dosage
40ml/daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01DB01" & MIKSTUR==1 // Cefaleksin.
FK og NLH: Normal dosage is 1-2g depended on infections and severity.
replace TREATMENTLENGTH=ORDINASJONANTALLPAKNINGER*VAREPAKNINGSTR/40 if ATCKODE=="J01EE01" &
MIKSTUR==1 // Sulfametoksazol og trimetoprim. FK: 40ml/daily except some indications
replace TREATMENTLENGTH=ORDINASJONANTALLPAKNINGER*VAREPAKNINGSTR*40/2000 if ATCKODE=="J01FA01"
& MIKSTUR==1 & VAREPAKNINGSTR==200 // Erytromycin. Abboticin 40mg/ml. FK: 2g/døgn.
replace TREATMENTLENGTH=ORDINASJONANTALLPAKNINGER*VAREPAKNINGSTR*100/2000 if
ATCKODE=="J01FA01" & MIKSTUR==1 & VAREPAKNINGSTR==100 // Erytromycin. Ery-Max 100mg/ml. FK:
2g/daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01FF01" & MIKSTUR==1 // Klindamycin.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="M01AE01" & MIKSTUR==1 // Ibuprofen.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AA01" & MIKSTUR==1 // Morfin.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AA05" & MIKSTUR==1 // Oksykodon.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02BE01" & MIKSTUR==1 // Paracetamol.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05CD08" & MIKSTUR==1 // Midazolam.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N06AB06" & MIKSTUR==1 // Sertralin.
FK og NLH: 50mg initially, can increase to 100 and 150mg.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="P01AB01" & MIKSTUR==1 //
Metronidazol.

// Creating an assumed treatment length of a drug dispensation for suppositories
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="M01AB01" & STIKKEPILLE==1 //
Indometacin. NLH: 50-100mg at night
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="M01AB05" & STIKKEPILLE==1 //
Diklofenak. FK: 750-150mg distributed to 2-3 times daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AA01" & STIKKEPILLE==1 // Morfin.
NLH: Usually 10-30mg every 4. hour
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AB02" & STIKKEPILLE==1 // Petidin.
FK: 100mg when needed. Can repeat after 3-4 hours up to 6 times daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AG02" & STIKKEPILLE==1 //
Ketobemidon og spasmolytika.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AJ06" & STIKKEPILLE==1 // Kodein
og paracetamol. FK: 1 suppository up to 4 times daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02BA01" & STIKKEPILLE==1 //
Acetylsalisylsyre.
replace TREATMENTLENGTH=ORDINASJONANTALLPAKNINGER*VAREPAKNINGSTR/3 if ATCKODE=="N02BE01" &
STIKKEPILLE==1 // Paracetamol. Expect they use 3 times daily.
replace TREATMENTLENGTH=90 if ATCKODE=="N02CA72" & STIKKEPILLE==1 // Ergotamin. Use for
migraine
replace TREATMENTLENGTH=90 if ATCKODE=="N02CC01" & STIKKEPILLE==1 // Sumatriptan.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05BA01" & STIKKEPILLE==1 //
Diazepam.FK: 5-10mg up to 3 times daily

// Creating an assumed treatment length of a drug dispensation for rectal fluid
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N05BA01" & REKVÆSKE==1 // Diazepam.

// Creating an assumed treatment length of a drug dispension for Oral sprays
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02BG10" & MUNNSPRAY==1 //
Cannabinoider.

// Creating an assumed treatment length of a drug dispension for single dose packets
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="A02BC05" & DOSEPOSER==1 //
Esomeprazol.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="C10AC01" & DOSEPOSER==1 //
Kolestyramin. FK: Varied dosage. 12-24mg daily
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="C10AC02" & DOSEPOSER==1 //
```

```
Kolestipol.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="J01XX05" & DOSEPOSER==1 // Metenamin.
FK: 1-2 dose packets daily
replace TREATMENTLENGTH=ORDINASJONANTALLPAKNINGER*VAREPAKNINGSTR if ATCKODE=="M01AX05" &
DOSEPOSER==1 // Glukosamin.
replace TREATMENTLENGTH=ORDINASJONANTALLDDD if ATCKODE=="N02AA01" & DOSEPOSER==1 // Morfin.
```

// Treatment episode construction

```
// Retrieving variables for date fecal sample taken and screening results
use "C:\T7 OG RESEPTREGISTERET\Legemidler og bærerskap\T7_data_20variabler - Kopi.dta"
keep PasientLopeNr_PDB2720 DATE_FECAL_SAMPLE_TAKEN_T7 KP_SENSU_LATU_SCAI_T7
save "C:\T7 OG RESEPTREGISTERET\Legemidler og bærerskap\T7_data_faecal_sample_taken.dta"
use "C:\T7 OG RESEPTREGISTERET\Legemidler og bærerskap\RReg_korr_20191101 - Kopi.dta"
merge m:1 PasientLopeNr_PDB2720 using "C:\T7 OG RESEPTREGISTERET\Legemidler og
bærerskap\T7_data_faecal_sample_taken.dta"
drop _merge

// Calculating the difference in number of days between dispensing date and date for fecal
sample taken.
gen DIFF_UTLEVERINGSDATO= UTLEVERINGSDATO-DATE_FECAL_SAMPLE_TAKEN_T7
sort PasientLopeNr_PDB2720 ATCKODE DIFF_UTLEVERINGSDATO
by PasientLopeNr_PDB2720 ATCKODE DIFF_UTLEVERINGSDATO: egen ORDINASJONANTALLDDD2=
sum(TREATMENTLENGTH)
by PasientLopeNr_PDB2720 ATCKODE DIFF_UTLEVERINGSDATO: egen ORDINASJONANTALLDDD3=
sum(ORDINASJONANTALLDDD)
keep PasientLopeNr_PDB2720 ATCKODE DIFF_UTLEVERINGSDATO ORDINASJONANTALLDDD2
DATE_FECAL_SAMPLE_TAKEN_T7 UTLEVERINGSDATO KP_SENSU_LATU_SCAI_T7 ORDINASJONANTALLDDD3
drop if KP_SENSU_LATU_SCAI_T7==.
duplicates drop

// Making lag and lead variables to take the difference between observations
by PasientLopeNr_PDB2720 ATCKODE: gen LAG_DATO = DIFF_UTLEVERINGSDATO[_n-1]
by PasientLopeNr_PDB2720 ATCKODE: gen LEAD_DATO = DIFF_UTLEVERINGSDATO[_n+1]
gen DELTA_DAGER = LEAD_DATO - DIFF_UTLEVERINGSDATO
recode DELTA_DAGER (.=0)

// Making lag and lead variables for DDD as well
by PasientLopeNr_PDB2720 ATCKODE: gen DDD=ORDINASJONANTALLDDD2
by PasientLopeNr_PDB2720 ATCKODE: gen LAG_DDD= ORDINASJONANTALLDDD2[_n-1]
by PasientLopeNr_PDB2720 ATCKODE: gen LEAD_DDD= ORDINASJONANTALLDDD2[_n+1]

// ADHERENCE 0.8 and creating lag and lead for DDD.
by PasientLopeNr_PDB2720 ATCKODE: gen DDD_80P_ADH= ORDINASJONANTALLDDD2/0.8
by PasientLopeNr_PDB2720 ATCKODE: gen LAG_DDD_80P_ADH= ORDINASJONANTALLDDD2[_n-1]/0.8
by PasientLopeNr_PDB2720 ATCKODE: gen LEAD_DDD_80P_ADH= ORDINASJONANTALLDDD2[_n+1]/0.8

// Create a variable for how long a prescription will cover the patient in days
by PasientLopeNr_PDB2720 ATCKODE: gen RESEPT_DEKNING_DAGER= DDD_80P_ADH - DELTA_DAGER
recode RESEPT_DEKNING_DAGER (min/0=0)

// Create a lag variable for prescription coverage period
by PasientLopeNr_PDB2720 ATCKODE: gen LAG_RESEPT_DEKNING_DAGER = RESEPT_DEKNING_DAGER[_n-1]
recode LAG_RESEPT_DEKNING_DAGER (.=0)

// Create carryover variable for the amount DDD left from previous dispense which can be
carried over to next
by PasientLopeNr_PDB2720 ATCKODE: gen CARRYOVER= ( DDD_80P_ADH - DELTA_DAGER) +
LAG_RESEPT_DEKNING_DAGER

// Create lag variable for carryover
by PasientLopeNr_PDB2720 ATCKODE: gen LAG_CARRYOVER = CARRYOVER[_n-1]

// Create treatment episode.
// 1= defines treatment episode start
gen TREATMENT_EPISODE = 0
replace TREATMENT_EPISODE=1 if LAG_CARRYOVER==.
replace TREATMENT_EPISODE = 1 if LAG_CARRYOVER < -14
```

```
// 3= defines treatment episode end
recode TREATMENT_EPISODE (0=3) if CARRYOVER < -14
recode TREATMENT_EPISODE (0=3) if LEAD_DATO==.

// Create a treatment_start variable
gen TREATMENT_START = DIFF_UTLEVERINGSDATO if TREATMENT_EPISODE==1
// Filling out missing values
by PasientLopeNr_PDB2720: replace TREATMENT_START = TREATMENT_START[_n-1] if
missing(TREATMENT_START)
replace TREATMENT_EPISODE = 3 if CARRYOVER < -14
replace TREATMENT_EPISODE = 3 if LEAD_DATO==.

// Create a treatment_end variable
gen TREATMENT_END = DIFF_UTLEVERINGSDATO + DDD_80P_ADH if TREATMENT_EPISODE==3
gsort PasientLopeNr_PDB2720 ATCKODE - DIFF_UTLEVERINGSDATO
// Filling out missing values
by PasientLopeNr_PDB2720: replace TREATMENT_END = TREATMENT_END[_n-1] if
missing(TREATMENT_END)

save "C:\T7 OG RESEPTREGISTERET\Legemidler og bærerskap\Rreg_treatment_episodes med variablene
for studiepopulasjon.dta"
```

// Multivariable logistic regressions

```
use "C:\T7 OG RESEPTREGISTERET\Legemidler og bærerskap\Rreg_treatment_episodes med variablene
for studiepopulasjon.dta", clear

// Create a variable that marks treatment episodes where a drug was dispensed after fecal
sampling. It's used for later calculation of DDD.
bysort PasientLopeNr_PDB2720 ATCKODE TREATMENT_START: gen code=1 if DIFF_UTLEVERINGSDATO[_N]>0

// Drop dispenses the same day and after fecal sampling. Dispenses before 180 days (non-
antibiotic) and 60 days (antibiotic)are also dropped.
drop if DIFF_UTLEVERINGSDATO>=0
drop if DIFF_UTLEVERINGSDATO<-180
drop if DIFF_UTLEVERINGSDATO<-60 & (substr(ATCKODE,1,3)=="J01" | substr(ATCKODE,1,3)=="P01")

// Create a variable that is supposed to calculate amount of days between last dispense before
fecal sampling and first dispense after fecal sampling.
bysort PasientLopeNr_PDB2720 ATCKODE TREATMENT_START: gen test=
DIFF_UTLEVERINGSDATO[_N]+DELTA_DAGER[_N]

// Sum total DDD from every treatment episodes
by PasientLopeNr_PDB2720 ATCKODE TREATMENT_START: egen total_ddd=sum(ORDINASJONANTALLDDD3)

// Fixing date of TREATMENT_START to the date for the first dispense within 180 days before
fecal sample. It's used to calculate new DDD for treatment episodes that last after fecal
sampling.
by PasientLopeNr_PDB2720 ATCKODE TREATMENT_START: replace
TREATMENT_START=DIFF_UTLEVERINGSDATO[1] if TREATMENT_START<-180

// 1 treatment episode per line
keep PasientLopeNr_PDB2720 ATCKODE total_ddd TREATMENT_START TREATMENT_END test code
duplicates drop

// Calculate new total DDD for treatment episodes that has a dispense before fecal sample that
also last after.
gen total_dager1=abs(TREATMENT_START)+TREATMENT_END if TREATMENT_END>0
gen fixed_total_ddd1=total_ddd/(total_dager1/abs(TREATMENT_START))

// Calculate a new total DDD for treatment episodes that has a dispense after fecal sample.
gen total_dager2=abs(TREATMENT_START)+test
gen fixed_total_ddd2=total_ddd/(total_dager2/abs(TREATMENT_START))

// Replacing new total DDD
replace total_ddd=fixed_total_ddd1 if TREATMENT_END>0
replace total_ddd=fixed_total_ddd2 if code==1
```

```
// Sum total DDD from every treatment episode to get a new total DDD a participant has used of
a drug.
by PasientLopeNr_PDB2720 ATCKODE: egen test_total_ddd=sum(total_ddd)
replace total_ddd=test_total_ddd

// Calculating amount of days a participant has used a drug
gen total_dager=abs(TREATMENT_START)-abs(TREATMENT_END)
replace total_dager=total_dager1 if TREATMENT_END>0
replace total_dager=total_dager2 if code==1
by PasientLopeNr_PDB2720 ATCKODE: egen test_total_dager=sum(total_dager)
replace total_dager=test_total_dager
keep PasientLopeNr_PDB2720 ATCKODE total_ddd total_dager
duplicates drop

// Creating drug groups based on ATC level 2.
gen atc2 = substr(ATCKODE,1,3)
drop ATCKODE

// Calculating amount of DDD and days a participant has used of a drug group
bysort PasientLopeNr_PDB2720 atc2: egen test_total_ddd=sum(total_ddd)
by PasientLopeNr_PDB2720 atc2: egen test_total_dager=sum(total_dager)
replace total_ddd=test_total_ddd
replace total_dager=test_total_dager
drop test_total_dager test_total_ddd
duplicates drop

// Create new variables for exposure. Total_ddd is the same. Daily_dosage is the amount of DDD
a participant uses daily.

levelsof atc2 , l(test) clean
foreach code in `test' {
        display "code = `code'"
        gen total_ddd_`code' = 0
        replace total_ddd_`code' = total_ddd if atc2=="`code'"
        bysort PasientLopeNr_PDB2720: egen max_total_ddd_`code'=max(total_ddd_`code')
        replace total_ddd_`code'=max_total_ddd_`code'
        drop max_total_ddd_`code'
        gen total_dager_`code' = 0
        replace total_dager_`code' = total_dager if atc2=="`code'"
        bysort PasientLopeNr_PDB2720: egen max_total_dager_`code'=max(total_dager_`code')
        replace total_dager_`code'=max_total_dager_`code'
        drop max_total_dager_`code'
        gen daily_dosage_`code'=total_ddd_`code'/total_dager_`code'
}

drop atc2 total_dager* total_ddd
duplicates drop

// Merge in variables that will be used for multivariable logistic regression.
merge 1:1 PasientLopeNr_PDB2720 using "C:\T7 OG RESEPTREGISTERET\Legemidler og
bærerskap\T7_data_20variabler - Kopi.dta"
drop if KP_SENSU_LATU_SCAI_T7==.
drop _merge

// Replacing missing values. Missing values= non-drug users
recode total_ddd_* (.=0)
recode daily_dosage_* (.=0)


// Dropping unnecessary variables
drop THYROXINE_T7 DIABETES_TABLETS_T7 ANALGESICS_ANTIINFLAM_T7 ACID_SUPRESSIVES_4WEEKS_T7
INSULIN_T7 LIPID_LOWERING_DRUGS_T7 ANTIBIOTICS_14DAYS_T7 ANTIBIOTICS_DAYS_SINCE_LAST_T7

// Fixing variables
recode SMOKE_DAILY_T7 (3=0)
recode ALCOHOL_UNITS_T7 (.=0) if ALCOHOL_FREQUENCY_T7==1
recode ALCOHOL_6UNITS_T7 (.=1) if ALCOHOL_FREQUENCY_T7==1
recode HOSPITAL_ADMISSION_TIMES_T7 (.=0)
```

```
// Grouping some variables
recode DIABETES_T7 (2=0)
recode BRONCHITIS_T7 (2=0)
replace HOSPITAL_ADMISSION_TIMES_T7=1 if HOSPITAL_ADMISSION_TIMES_T7>0
recode ALCOHOL_FREQUENCY_T7 (4=3) (5=4)
recode ALCOHOL_UNITS_T7 (2=1) (5=2) (4=2) (3=2)
recode ALCOHOL_6UNITS_T7 (5=4)
recode SMOKE_DAILY_T7 (2=0)

// Multivariable logistic regression
logistic KP_SENSU_LATU_SCAI_T7 total_ddd_A02 total_ddd_A10 total_ddd_C10 total_ddd_H03
total_ddd_J01 total_ddd_M01 total_ddd_N02 total_ddd_N05 total_ddd_N06 total_ddd_P01 AGE_T7
i.DIABETES_T7 i.BRONCHITIS_T7 i.HOSPITAL_ADMISSION_TIMES_T7 i.ALCOHOL_FREQUENCY_T7
i.ALCOHOL_UNITS_T7 i.ALCOHOL_6UNITS_T7 i.SMOKE_DAILY_T7 i.CROHNS_COLITIS_T7

// Logistic regression diagnostics
**Goodness of fit**
lfit, group(10) table // Hosmer and Lemeshow's goodness of fit test
**collinearity**
collin total_ddd_A02 total_ddd_A10 total_ddd_C10 total_ddd_H03 total_ddd_J01 total_ddd_M01
total_ddd_N02 total_ddd_N05 total_ddd_N06 total_ddd_P01 AGE_T7 DIABETES_T7 BRONCHITIS_T7
HOSPITAL_ADMISSION_TIMES_T7 ALCOHOL_FREQUENCY_T7 ALCOHOL_UNITS_T7 ALCOHOL_6UNITS_T7
SMOKE_DAILY_T7 CROHNS_COLITIS_T7, corr
**outliers**
gen id=_n
predict p // probability.
predict r, rstand //  Pearson residual
scatter r id, mlabel(PasientLopeNr_PDB2720) // Index plot Pearson residual
scatter r p, mlabel(PasientLopeNr_PDB2720) ylab(-4(2) 6) yline(0)
predict dv, dev // Deviance residual
scatter dv id, mlab(PasientLopeNr_PDB2720) // Index plot deviance residual
predict hat, hat // Pregibon leverage
scatter hat id, mlab(PasientLopeNr_PDB2720) // Index plot pregibon leverage
scatter r hat, mlab(PasientLopeNr_PDB2720) yline(0) xlab(0(0.1)0.6) // Pearson vs Pregibon
leverage
predict dbeta, dbeta // Pregibon's dbeta.
scatter dbeta PasientLopeNr_PDB2720, mlab(PasientLopeNr_PDB2720)

// Multivariable logistic regression for daily dosage/intensity
logistic KP_SENSU_LATU_SCAI_T7 daily_dosage_* AGE_T7 i.DIABETES_T7 i.BRONCHITIS_T7
i.HOSPITAL_ADMISSION_TIMES_T7 i.ALCOHOL_FREQUENCY_T7 i.ALCOHOL_UNITS_T7 i.ALCOHOL_6UNITS_T7
i.SMOKE_DAILY_T7 i.CROHNS_COLITIS_T7

// Logistic regression diagnostics
**Goodness of fit**
lfit, group(10) table // Hosmer and Lemeshow's goodness of fit test
**collinearity**
collin daily_dosage_* AGE_T7 DIABETES_T7 BRONCHITIS_T7 HOSPITAL_ADMISSION_TIMES_T7
ALCOHOL_FREQUENCY_T7 ALCOHOL_UNITS_T7 ALCOHOL_6UNITS_T7 SMOKE_DAILY_T7 CROHNS_COLITIS_T7, corr
**outliers**
drop p r dbeta hat
predict p // probability.
predict r, rstand // residual
scatter r p, mlabel(PasientLopeNr_PDB2720) ylab(-4(2)6) yline(0) xlab(0(0.1)0.7)
predict hat, hat // Pregibon leverage
scatter r p, mlab(PasientLopeNr_PDB2720)
scatter r hat, mlab(PasientLopeNr_PDB2720) yline(0)
predict dbeta, dbeta // Pregibon's dbeta.
scatter dbeta PasientLopeNr_PDB2720, mlab(PasientLopeNr_PDB2720)
```

// Cumulative change

```
use "C:\T7 OG RESEPTREGISTERET\Legemidler og bærerskap\Rreg_treatment_episodes med variablene
for studiepopulasjon.dta", clear


// Creating drug groupings based on ATC level 2
gen atc2 = substr(ATCKODE,1,3)
keep PasientLopeNr_PDB2720 KP_SENSU_LATU_SCAI_T7 TREATMENT_END TREATMENT_START atc2
duplicates drop
```

```
// Can adjust this to look at the preferred drug group
keep if atc2=="J01" | atc2=="A07" | atc2=="P01"

// Making negative values to positive to use the function at(). Dropping those who dispensed
after fecal sampling.
gen test= TREATMENT_END*-1
drop if TREATMENT_START>0
egen month_rx=cut (test), at(1,30,60,90,120,150,180,210,240,270,300,330,360,5000) icodes
recode month_rx (0=1) (1=2) (2=3) (3=4) (4=5) (5=6) (6=7) (7=8) (8=9) (9=10) (10=11) (11=12)
(12=13) (.=0)

// Merging with a file that only containts patient id and screening result for the study
population. Merge==2 are those who are dropped. They will be place in month_rx=13 which
contains non-drug users.
merge m:1 PasientLopeNr_PDB2720 using "C:\T7 OG RESEPTREGISTERET\Legemidler og
bærerskap\Pasientlopenummer.dta"
replace month_rx=13 if _merge==2

// Keeping last treatment episode by sorting in the order to get the last treatment episode at
the top
sort PasientLopeNr_PDB2720 test
by PasientLopeNr_PDB2720: keep if _n==1

// Create a variable "num", which represents the number of participants that has atleast 1
prescription that specific month.
bysort month_rx: egen num=count(PasientLopeNr_PDB2720)

// Create variable "num_pos", that represents the number of participants in "num" that has
positive result from fecal screening
bysort month_rx: egen num_pos=count( PasientLopeNr_PDB2720 ) if KP_SENSU_LATU_SCAI_T7==1
bysort month_rx: egen num_pos_max=max(num_pos)
drop num_pos
rename num_pos_max num_pos
keep month_rx num num_pos
duplicates drop

// Replacing missing values due to foreach will produce missing values.
replace num_pos=0 if num_pos==.
replace num=0 if num==.

foreach l of numlist 1(1)12 {
        replace num = num + num[_n-1] if month_rx==`l'
        replace num_pos = num_pos + num_pos[_n-1] if month_rx==`l'
}

gen low = .
gen high = .
gen prop_pos = num_pos / num
format prop_pos %9.2f
foreach mnt of numlist 0(1)12 {
        quietly sum num if month_rx==`mnt'
        local num = r(mean)
        quietly sum num_pos if month_rx==`mnt'
        local num_pos = r(mean)
        quietly cii proportions `num' `num_pos', exact
        local low = r(lb)
        local high = r(ub)
        replace low = `low' if month_rx==`mnt'
        replace high = `high' if month_rx==`mnt'
}

replace prop_pos=prop_pos*100
replace high=high*100
replace low=low*100

quietly mean prop_pos if month_rx==13
mat b=e(b)
local test=b[1,1]
```

```
twoway (rarea low high month_rx if month_rx<13, col(gs12) lw(none)) ///
(scatter  prop_pos month_rx if month_rx<13, mc(gs0) ylabel(0(10)50) yline(`test') ///
c(l) lc(gs9)xlabel(0(1)12) mlabel(prop_pos) mlabposition(1) mlabc(gs0) mlabs(vsmall) ///
text(14.17 3.5 "Proportion of carriers in the non-antibiotic using population", c(black)
si(vsmall))), ///
legend(off) xtitle("Months between last drug use and faeces sample") ytitle("Proportion of
carriers (%)") ///
title("Antibiotics")
```

// Clustering

```
use "C:\T7 OG RESEPTREGISTERET\Legemidler og bærerskap\Rreg_treatment_episodes med variablene
for studiepopulasjon.dta"

// Replacing to missing values for treatment episode that started after fecal sampling and
treatment episodes that ended 90 days before fecal sampling
replace ATCKODE="" if TREATMENT_END<-90
replace ATCKODE="" if TREATMENT_START>0

// Creating drug groups based on ATC level 2
gen atc2 = substr(ATCKODE,1,3)
capture drop test_*
capture drop max_*

// Creating variables for the drug groups
levelsof atc2 , l(test) clean

foreach code in `test' {
       display "code = `code'"
       gen test_`code' = 0
       recode test_`code' (0=1) if atc2=="`code'"
       bysort PasientLopeNr_PDB2720: egen max_`code' = max(test_`code')
}
drop test_*
keep PasientLopeNr_PDB2720 max_*
duplicates drop

// Create a variable that sums up antibiotic use (J01,P01). None used A07
recode max_J01 (0=1) if max_P01==1
drop max_P01
rename max_J01 max_J01_P01

// Merge with dataset from Tromsø 7
merge 1:1 PasientLopeNr_PDB2720 using "C:\T7 OG RESEPTREGISTERET\Legemidler og
bærerskap\T7_data_20variabler - Kopi.dta"
drop if _merge==2

// Clustering
local list1 max_A02 max_A10 max_C10 max_H03 max_J01_P01 max_M01 max_N02 max_N05 max_N06
forvalues k = 1(1)20 {

cluster kmeans `list1', k(`k') measure(jaccard) start(random(123)) name(cs`k')
}

//WSS matrix
matrix WSS = J(20,5,.)
matrix colnames WSS = k WSS log(WSS) eta-squared PRE

//WSS for each clustering
forvalues k = 1(1)20 {
scalar ws`k' = 0
foreach v in `list1' {
quietly anova `v' cs`k'
scalar ws`k' = ws`k' + e(rss)
}
matrix WSS[`k', 1] = `k'
matrix WSS[`k', 2] = ws`k'
matrix WSS[`k', 3] = log(ws`k')
matrix WSS[`k', 4] = 1 - ws`k'/WSS[1,2]
```

```
matrix WSS[`k', 5] = (WSS[`k'-1,2] - ws`k'')/WSS[`k'-1,2]
}

matrix list WSS
local squared = char(178)
_matplot WSS, columns(2 1) connect(l) xlabel(#10) name(plot1, replace) nodraw noname
_matplot WSS, columns(3 1) connect(l) xlabel(#10) name(plot2, replace) nodraw noname
_matplot WSS, columns(4 1) connect(l) xlabel(#10) name(plot3, replace) nodraw noname
ytitle({&eta}`squared'')
_matplot WSS, columns(5 1) connect(l) xlabel(#10) name(plot4, replace) nodraw noname

// Making graph
graph combine plot1 plot2 plot3 plot4, name(plot1to4, replace)

// Table for clusters
tabstat max_A02 max_A10 max_C10 max_H03 max_J01_P01 max_M01 max_N02 max_N05 max_N06 , by(cs7)

// K. pneumoniae prevalence among clusters
tabstat KP_SENSU_LATU_SCAI_T7, by(cs7)

// Making radarplot
preserve
collapse max_A02 max_A10 max_C10 max_H03 max_J01_P01 max_M01 max_N02 max_N05 max_N06 , by(cs7)
radar cs7 max_A02 max_A10 max_C10 max_H03 max_J01_P01 max_M01 max_N02 max_N05 max_N06
restore

// Making another radarplot
collapse max_A02 max_A10 max_C10 max_H03 max_J01_P01 max_M01 max_N02 max_N05 max_N06 , by(cs7)
reshape long max_, i(cs7) j(ATC_level2, string)
list if cs7==2
reshape wide max_, i(ATC_level2) j(cs7)
rename (max_#) (Cluster#)
collapse max_A02 max_A10 max_C10 max_H03 max_J01_P01 max_M01 max_N02 max_N05 max_N06 , by(cs7)
radar ATC_level2 Cluster1 Cluster2 Cluster3 Cluster4 Cluster5 Cluster6 Cluster7
```

Appendix 2: Variables description

Variable name	Variable description	Variable type	Comments	
PasientLopeNr_PDB2720	Patient's anonymous ID	Numeric (long)	Central variable	Dataset from NorPD
PASIENTKJONN	Patient's sex	Numeric (byte)		
PASIENTDODSAR	Patient's death year	Numeric (int.)		
PASIENTDODSMND	Patient's death month	Numeric (byte)		
OrdinasjonLopeNr	Prescription number	Numeric (long)		
UTLEVERINGSDATO	Dispense date	Numeric (int.)	Central variable	
ORDINASJONANTALLPAKNINGER	No. Of packages dispensed	Numeric (int.)		
ORDINASJONAUP	Cost of dispense	Numeric (long)		
ORDINASJONANTALLDDD	Total DDD dispensed	Numeric (long)	Central variable	
VARENR	Medicine's registration number	Numeric (long)		
VARENAVN	Medicine's name	String (str31)		
VAREPAKNING	Package size	String (str5)		
VAREPAKNINGENHET	Concentration In units for package (e.g. gram)	String (str5)		
VAREPAKNINGSTYRKE	Medicine's strength	String (str10)		
ATCKODE	ATC code	String (str7)	Central variable	
AtcKodeDDDVerdi	DDD for the ATC code	Numeric (long)		
AtcKodeDDDEnhet	Concentration in units for ATC code (e.g. gram)	String (str4)		
AGE_T7[a]	Age per 31.12.2015	Numeric (double)	Central variable	Dataset from
ANTIBIOTICS_14DAYS_T7	Taken any antibiotics last 14 days?	Numeric (double)		
ANTIBIOTICS_DAYS_SINCE_LAST_T7	How many days since last if taken antibiotic last 14 days	Numeric (double)		
DATE_FECAL_SAMPLE_TAKEN_T7	Fecal sample date	Numeric (long)	Central variable	
KP_SENSU_LATU_SCAI_T7	Screening result of *K. pneumoniae*	Numeric (double)	Central variable	
DIABETES_T7[a]	Diabetes? (yes/no)	Numeric (double)	Central variable	
BRONCHITIS_T7[a]	Have/had chronic bronchitis/emphysema/COPD? (yes/no)	Numeric (double)	Central variable	

HOSPITAL_ADMISSION_TIMES_T7[a]	Hospital last 12 months? How many?	Numeric (double)	Central variable	
LIPID_LOWERING_DRUGS_T7	Use cholesterol-lowering drugs?	Numeric (double)		
INSULIN_T7	Use insulin?	Numeric (double)		
DIABETES_TABLETS_T7	Use tablets for diabetes?	Numeric (double)		
THYROXINE_T7	Use drugs for hypothyroidism?	Numeric (double)		
ACID_SUPRESSIVES_4WEEKS_T7	How often is acid suppressive drugs used last 4 weeks?	Numeric (double)		
ALCOHOL_FREQUENCY_T7[a]	How often do you drink alcohol?	Numeric (double)	Central variable	
ALCOHOL_UNITS_T7[a]	how many units of alcohol in one occasion?	Numeric (double)	Central variable	
ALCOHOL_6UNITS_T7[a]	How often do you drink 6 or more units of alcohol in one occasion	Numeric (double)	Central variable	
SMOKE_DAILY_T7[a]	Do/did you smoke daily?	Numeric (double)	Central variable	
CROHNS_COLITIS_T7[a]	Do you have Crohn's disease/ulcerous colitis?	Numeric (double)	Central variable	
ANALGESICS_ANTIINFLAM_T7	Used any analgesics or anti-inflammatory drugs regularly in the past?	Numeric (double)		

Some variables were left out as they were unnecessary such as variables for reimbursement
[a]Variables adjusted for in logistic regressions. Some were modified such as "hospital admission times", as original variable counted how many times participant was hospitalized. It was modified to yes/no to being hospitalized last 12 months.

Appendix 3: List of assumed duration for every drug

Drug groups and actives substances	ATC	Formulation	Assumed dosage regimen
Antacid (A02)			
Ordinary salt combination (Novaluzid)	A02AD01	Tablet	Drug dispensation lasts 90 days
Antacids with sodium bicarbonate	A02AH	Tablet	Drug dispensation lasts 90 days
Ranitidine	A02BA02	Tablet	1 DDD daily
Famotidine	A02BA03	Tablet	1 DDD daily
Misoprostol	A02BB01	Tablet	3 tablets daily
Omeprazole	A02BC01	Tablet	1 tablet daily
Pantoprazole	A02BC02	Tablet	1 tablet daily
		Injection	1 vial daily
Lansoprazole	A02BC03	Tablet	1 tablet daily
Esomeprazole	A02BC05	Tablet	1 tablet daily
		Dose packet	1 DDD daily
Sucralfate	A02BX02	Tablet	3 tablets daily
		Liquid	1 DDD daily
Alginic acid	A02BX13	Tablet	1 DDD daily
		Liquid	1 DDD daily
Antibiotics (A07)			
Vancomycin	A07AA09	Tablet	4 tablets daily
Antidiabetics (A10)			
Insulin (human)	A10AB01	Injection	Drug dispensation lasts 90 days
Insulin lispro	A10AB04	Injection	Drug dispensation lasts 90 days
Insulin aspart	A10AB05	Injection	Drug dispensation lasts 90 days
Insulin glulisine	A10AB06	Injection	Drug dispensation lasts 90 days
Insulin (human)	A10AC01	Injection	Drug dispensation lasts 90 days
Insulin aspart	A10AD05	Injection	Drug dispensation lasts 90 days
Insulin glargine	A10AE04	Injection	Drug dispensation lasts 90 days
Insulin determir	A10AE05	Injection	Drug dispensation lasts 90 days
Insulin degludec	A10AE06	Injection	Drug dispensation lasts 90 days
Metformin	A10BA02	Tablet	Drug dispensation lasts 90 days
Glibenclamide	A10BB01	Tablet	Drug dispensation lasts 90 days
Glipizide	A10BB07	Tablet	Drug dispensation lasts 90 days
Glimepiride	A10BB12	Tablet	1 tablet daily
Metformin and sitagliptin	A10BD07	Tablet	2 tablets daily
Metformin and vildagliptin	A10BD08	Tablet	2 tablets daily
Metformin and linagliptin	A10BD11	Tablet	2 tablets daily
Acarbose	A10BF01	Tablet	3 tablets daily
Pioglitazone	A10BG03	Tablet	1 tablet daily
Sitagliptin	A10BH01	Tablet	1 tablet daily

Vildagliptin	A10BH02	Tablet	Drug dispensation lasts 90 days
Saxagliptin	A10BH03	Tablet	1 tablet daily
Linagliptin	A10BH05	Tablet	1 tablet daily
Exenatide	A10BJ01	Injection	Bydureon: 1 injection weekly. Byetta: 2 injections daily
Liraglutide	A10BJ02	Injection	1 DDD daily
Dulaglutide	A10BJ05	Injection	1 injection daily
Dapagliflozin	A10BK01	Tablet	1 tablet daily
Empagliflozin	A10BK03	Tablet	1 tablet daily
Repaglinide	A10BX02	Tablet	Drug dispensation lasts 90 days
Lipid-modifying drugs (C10)			
Red yeast rice (a natural medicine)	C10	Tablet	4 tablets daily
Simvastatin	C10AA01	Tablet	1 tablet daily
Lovastatin	C10AA02	Tablet	1 tablet daily
Pravastatin	C10AA03	Tablet	1 tablet daily
Fluvastatin	C10AA04	Tablet	1 tablet daily
Atorvastatin	C10AA05	Tablet	1 tablet daily
Rosuvastatin	C10AA07	Tablet	1 tablet daily
Colestyramine	C10AC01	Tablet	1 tablet daily
		Dose packet	1 DDD daily
Colestipol	C10AC02	Tablet	1 tablet daily
		Dose packet	1 DDD daily
Colesevelam	C10AC04	Tablet	Drug dispensation lasts 90 days
Omega-3-triglycerides incl. other esters and acids	C10AX06	Tablet	Drug dispensation lasts 90 days
Ezetimibe	C10AX09	Tablet	1 tablet daily
Evolocumab	C10AX13	Injection	1 injection daily
Simvastatin and ezetimibe	C10BA02	Tablet	1 tablet daily
Atorvastatin and ezetimibe	C10BA05	Tablet	1 tablet daily
Thyroid drugs (H03)			
Levothyroxine sodium	H03AA01	Tablet	1 tablet daily
Liothyronine sodium	H03AA02	Tablet	1 DDD daily
Thyroid gland preparations	H03AA05	Tablet	Drug dispensation lasts 90 days
Antibiotics (J01)			
Doxycycline	J01AA02	Tablet	1 DDD daily
Lymecycline	J01AA04	Tablet	1 DDD daily
Tetracycline	J01AA07	Tablet	1 DDD daily
Amoxicillin	J01CA04	Tablet	1 DDD daily
		Liquid	1 DDD daily
Pivmecillinam	J01CA08	Tablet	3 tablets daily
Phenoxymethylpenicillin	J01CE02	Tablet	4 tablets daily
		Liquid	10ml drops daily or 40ml mixture daily

Dicloxacillin	J01CF01	Tablet	1 DDD daily
Cloxacillin	J01CF02	Tablet	1 DDD daily
		Injection	1 DDD daily
Cefalexin	J01DB01	Tablet	1 DDD daily
		Liquid	1 DDD daily
Cefuroxime	J01DC02	Tablet	1 DDD daily
Cefotaxime	J01DD01	Injection	Drug dispensation lasts 90 days
Trimethoprim	J01EA01	Tablet	1 DDD daily
Sulfamethoxazole/trimethoprim	J01EE01	Tablet	1 DDD daily
		Liquid	40ml daily
Erythromycin	J01FA01	Tablet	1 DDD daily
		Liquid	2 gram daily. There are 40mg/ml and 100mg/ml packages
Clarithromycin	J01FA09	Tablet	1 DDD daily
Azithromycin	J01FA10	Tablet	1 DDD daily
Clindamycin	J01FF01	Tablet	4 tablets daily
		Liquid	1 DDD daily
Oflocaxin	J01MA01	Tablet	2 tablets daily
Ciprofloxacin	J01MA02	Tablet	2 tablets daily
Levofloxacin	J01MA12	Tablet	1 DDD daily
Moxifloxacin	J01MA14	Tablet	1 DDD daily
Fusidic acid	J01XC01	Tablet	1 DDD daily
Nitrufurantoin	J01XE01	Tablet	1 DDD daily
Methenamine	J01XX05	Tablet	2 tablets daily
		Dose packet	1 DDD daily
Linezolid	J01XX08	Tablet	2 tablets daily
Anti-inflammatory/antirheumatic drugs (M01)			
Indometacin	M01AB01	Tablet	1 DDD daily
		Suppository	1 DDD daily
Diclofenac	M01AB05	Tablet	1 DDD daily
		Injection	1 DDD daily
		Suppository	1 DDD daily
Diclofenac, combinations	M01AB55	Tablet	1 DDD daily
Piroxicam	M01AC01	Tablet	1 tablet daily
Meloxicam	M01AC06	Tablet	1 tablet daily
Ibuprofen	M01AE01	Tablet	Normal tablets: 4 tablets daily. Depot tablets: 2 tablets daily
		Liquid	1 DDD daily
Naproxen	M01AE02	Tablet	2 tablets daily
Ketoprofen	M01AE03	Tablet	1 DDD daily. Dispense 200mg = use 1 tablet daily
Naproxen and esomeprazole	M01AE52	Tablet	1 DDD daily
Tolfenamic acid	M01AG02	Tablet	Drug dispensation lasts 90 days

Celecoxib	M01AH01	Tablet	1 DDD daily
Etoricoxib	M01AH05	Tablet	1 tablet daily
Glucosamine and chondroitin	M01AX	Tablet	3 tablets daily
Nabumetone	M01AX01	Tablet	1 DDD daily
Glucosamine	M01AX05	Tablet	1 tablet daily. Dispense 400mg = use 3 tablets daily
		Dose packet	1 packet daily
Auranofin	M01CB03	Tablet	2 tablets daily
Analgesics (N02)			
Morphine	N02AA01	Tablet	1 DDD daily
		Injection	1 DDD daily
		Liquid	1 DDD daily
		Suppository	1 DDD daily
		Dose packet	1 DDD daily
Oxycodone	N02AA05	Tablet	1 DDD daily
		Injection	1 DDD daily
		Liquid	1 DDD daily
Oxycodone and naloxone	N02AA55	Tablet	1 DDD daily
Ketobemidone	N02AB01	Tablet	1 DDD daily
Pethidine	N02AB02	Tablet	1 tablet daily
		Suppository	1 DDD daily
Fentanyl	N02AB03	Tablet	1 DDD daily
		Patch	1 patch every 3. day
Buprenorphine	N02AE01	Tablet	1 DDD daily
		Patch	1 patch every week
Ketobemidone and antispasmodics	N02AG02	Tablet	1 tablet daily
		Suppository	1 DDD daily
Codeine and paracetamol	N02AJ06	Tablet	1 DDD daily
		Suppository	1 DDD daily
Codeine and acetylsalicylic acid	N02AJ07	Tablet	1 DDD daily
Tramadol and paracetamol	N02AJ13	Tablet	1 DDD daily
Tramadol	N02AX02	Tablet	1 DDD daily
Tapentadol	N02AX06	Tablet	1 DDD daily
Acetylsalicylic acid	N02BA01	Tablet	1 DDD daily
		Suppository	1 DDD daily
Phenazone, combin excl. psycholeptics	N02BB51	Tablet	1 DDD daily
Paracetamol	N02BE01	Tablet	3 tablets daily
		Liquid	1 DDD daily
		Suppository	3 suppository daily
Paracetamol, combin excl. psycholeptics	N02BE51	Tablet	1 DDD daily
Cannabinoids	N02BG10	Oral spray	1 DDD daily

Ergotamine, combin with psycholeptics	N02CA72	Tablet	Drug dispensation lasts 90 days
		Suppository	Drug dispensation lasts 90 days
Sumatriptan	N02CC01	Tablet	Drug dispensation lasts 90 days
		Injection	Drug dispensation lasts 90 days
		Nasal	Drug dispensation lasts 90 days
		Suppository	Drug dispensation lasts 90 days
Naratriptan	N02CC02	Tablet	Drug dispensation lasts 90 days
Zolmitriptan	N02CC03	Tablet	Drug dispensation lasts 90 days
		Nasal	Drug dispensation lasts 90 days
Rizatriptan	N02CC04	Tablet	Drug dispensation lasts 90 days
Almotriptan	N02CC05	Tablet	Drug dispensation lasts 90 days
Eletriptan	N02CC06	Tablet	Drug dispensation lasts 90 days
Frovatriptan	N02CC07	Tablet	Drug dispensation lasts 90 days
Clonidine	N02CX02	Tablet	2 tablets daily
Psycholeptics (N05)			
Chlorpromazine	N05AA01	Tablet	Drug dispensation lasts 90 days
Levomepromazine	N05AA02	Tablet	Drug dispensation lasts 90 days
Perphenazine	N05AB03	Tablet	1 DDD daily
Prochlorperazine	N05AB04	Tablet	1 DDD daily
Haloperidol	N05AD01	Tablet	1 DDD daily
		Injection	1 DDD daily
Chlorprothixene	N05AF03	Tablet	1 DDD daily
Zuclopenthixol	N05AF05	Tablet	1 DDD daily
Clozapine	N05AH02	Tablet	1 DDD daily
Olanzapine	N05AH03	Tablet	1 tablet daily
		Injection	1 injection every 2. week
Quetiapine	N05AH04	Tablet	1 DDD daily
Lithium	N05AN01	Tablet	1 DDD daily
Risperidone	N05AX08	Tablet	1 DDD daily
Aripiprazole	N05AX12	Tablet	1 tablet daily
Diazepam	N05BA01	Tablet	1 DDD daily
		Injection	1 DDD daily
		Rectal fluid	1 DDD daily
Oxazepam	N05BA04	Tablet	1 DDD daily
Alprazolam	N05BA12	Tablet	3 tablets daily. Depot tablets: 1-2 tablets daily
Hydroxyzine	N05BB01	Tablet	2 tablets daily
Buspirone	N05BE01	Tablet	1 DDD daily
Nitrazepam	N05CD02	Tablet	1 DDD daily
Flunitrazepam	N05CD03	Tablet	1 DDD daily
Midazolam	N05CD08	Injection	1 DDD daily
		Liquid	1 DDD daily

Zopiclone	N05CF01	Tablet	1 tablet daily
Zolpidem	N05CF02	Tablet	1 tablet daily
Melatonin	N05CH01	Tablet	1 tablet daily
Chlomethiazole	N05CM02	Tablet	1 DDD daily
Psychoanaleptics (N06)			
Chlomipramine	N06AA04	Tablet	1 DDD daily
Opipramol	N06AA05	Tablet	1 DDD daily
Trimipramine	N06AA06	Tablet	1 DDD daily
Amitriptyline	N06AA09	Tablet	1 DDD daily
Nortriptyline	N06AA10	Tablet	1 DDD daily
Doxepin	N06AA12	Tablet	1 DDD daily
Fluoxetine	N06AB03	Tablet	1 DDD daily
Citalopram	N06AB04	Tablet	1 DDD daily
Paroxetine	N06AB05	Tablet	1 DDD daily
Sertraline	N06AB06	Tablet	1 DDD daily
		Liquid	1 DDD daily
Fluvoxamine	N06AB08	Tablet	1 DDD daily
Escitalopram	N06AB10	Tablet	1 tablet daily
Moclobemide	N06AG02	Tablet	2 tablets daily
Mianserin	N06AX03	Tablet	1 tablet daily
Mirtazapine	N06AX11	Tablet	1 DDD daily
Bupropion	N06AX12	Tablet	1 tablet daily
Venlafaxine	N06AX16	Tablet	1 DDD daily
Reboxetine	N06AX18	Tablet	1 DDD daily
Duloxetine	N06AX21	Tablet	1 DDD daily
Vortioxetine	N06AX26	Tablet	1 tablet daily
Dexamfetamine	N06BA02	Tablet	1 DDD daily
Methylphenidate	N06BA04	Tablet	1 DDD daily
Modafinil	N06BA07	Tablet	1 DDD daily
Atomoxetine	N06BA09	Tablet	1 tablet daily
Lisdexamfetamine	N06BA12	Tablet	1 tablet daily
Caffeine	N06BC01	Tablet	1 DDD daily
Piracetam	N06BX03	Tablet	1 DDD daily
Donepezil	N06DA02	Tablet	1 tablet daily
Rivastigmine	N06DA03	Tablet	2 tablets daily
		Patch	1 patch daily
Memantine	N06DX01	Tablet	1 tablet daily
Antibiotics (P01)			
Metronidazole	P01AB01	Tablet	1 DDD daily
		Liquid	1 DDD daily

Appendix 4: Model diagnostics for multivariable logistic regression

Diagnostics for total exposure in DDD and *K. pneumoniae* carriage

Number of observations = 2684
Number of groups = 10
Hosmer-Lemeshow chi2(8) = 4.79
Prob > chi = 0.7794

Group	Probability	Observed 1	Expected 1	Observed 0	Expected 0	Total
1	0.1087	16	24.0	253	245.0	269
2	0.1265	37	32.0	231	236.0	268
3	0.1377	39	35.7	230	233.3	269
4	0.1454	39	38.0	229	230.0	268
5	0.1543	38	40.2	230	227.8	268
6	0.1620	45	42.5	224	226.5	269
7	0.1716	43	45.8	232	229.2	275
8	0.1853	48	46.6	214	215.4	262
9	0.2231	54	53.7	214	214.3	268
10	0.6549	78	78.5	190	189.5	268

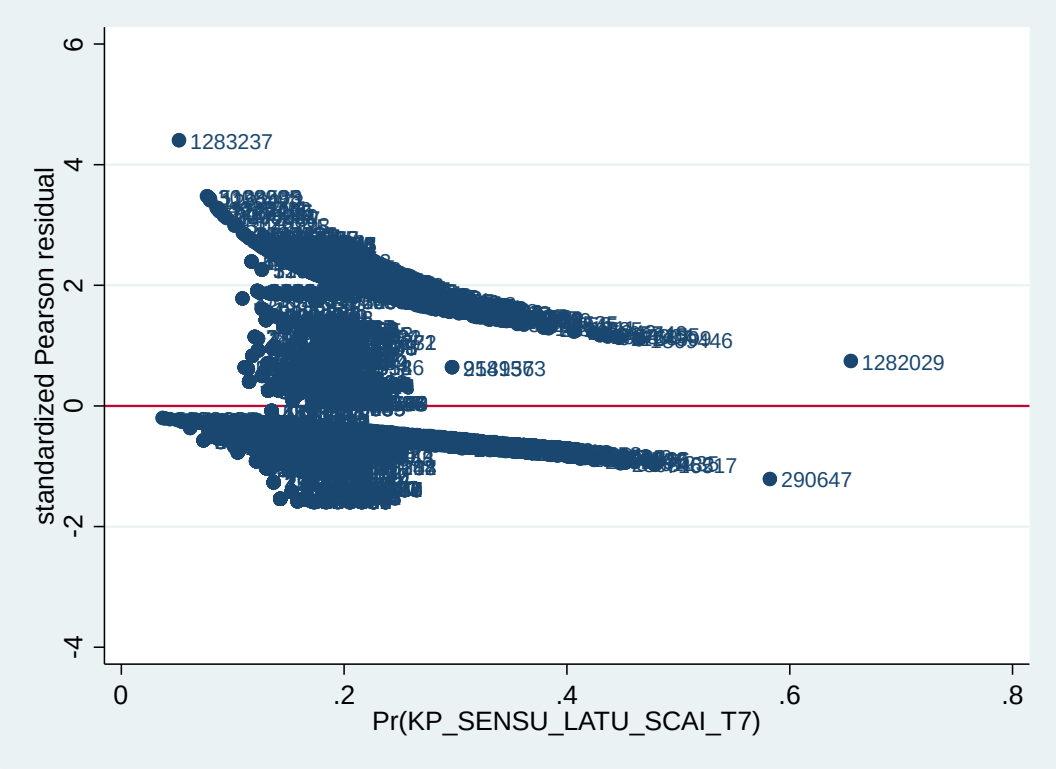
A Hosmer-Lemeshow's goodness of fit test is a commonly used diagnostic and shortly explained, the more alike the observed and expected values are, the better the fit. With a p-value of 0.78 in the Hosmer-Lemeshow's goodness of fit test, there are no significant difference between the observed and expected values, which is a good sign for our model

Collinearity diagnostics

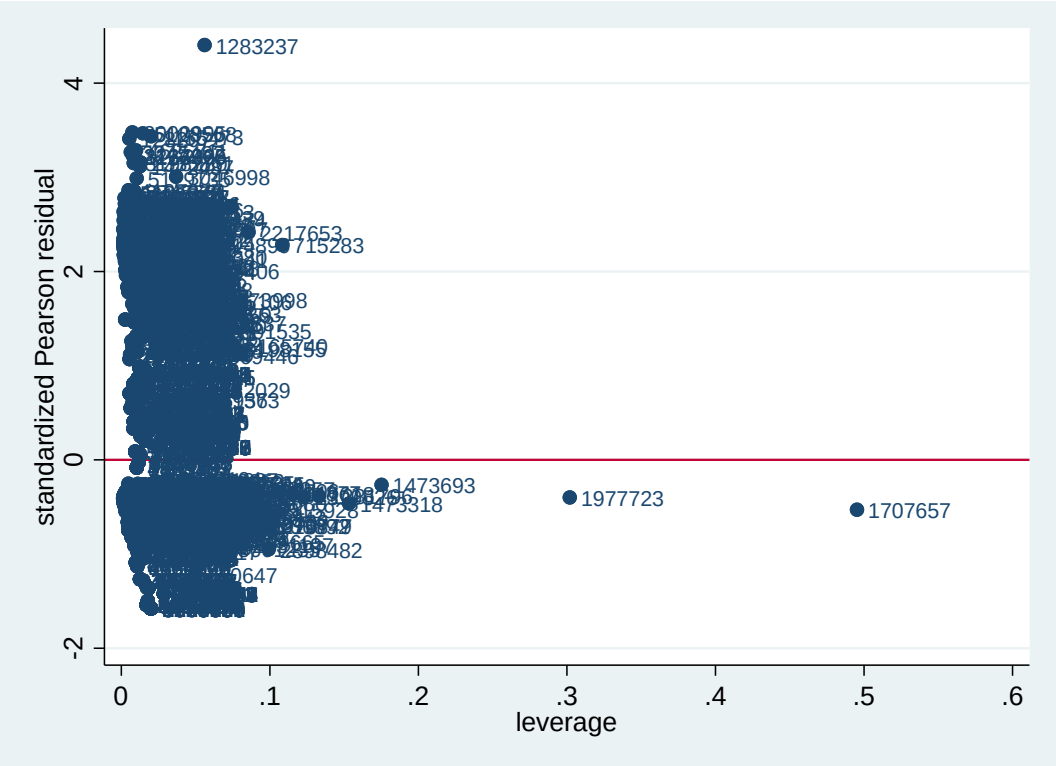
Variable	VIF	SQRT VIF	Tolerance	R-Squared	Eigenval	Cond Index
total_ddd_A02	1.06	1.03	0.9435	0.0565	2.1197	1.0000
total_ddd_A10	2.05	1.43	0.4879	0.5121	1.6943	1.1185
total_ddd_C10	1.06	1.03	0.9414	0.0586	1.4268	1.2189
total_ddd_H03	1.01	1.00	0.9901	0.0099	1.2886	1.2826
total_ddd_J01	1.06	1.03	0.9439	0.0561	1.1786	1.3411
total_ddd_M01	1.07	1.04	0.9315	0.0685	1.0908	1.3940
total_ddd_N02	1.10	1.05	0.9096	0.0904	1.0484	1.4219
total_ddd_N05	1.07	1.03	0.9369	0.0631	1.0144	1.4456
total_ddd_N06	1.01	1.01	0.9870	0.0130	0.9744	1.4749
total_ddd_P01	1.04	1.02	0.9583	0.0417	0.9541	1.4906
AGE_T7	1.15	1.07	0.8683	0.1317	0.9177	1.5198
DIABETES_T7	2.07	1.44	0.4827	0.5173	0.8545	1.5750
BRONCHITIS_T7	1.03	1.02	0.9690	0.0310	0.8511	1.5781
HOSPITAL_ADMISSION_TIMES_T7	1.04	1.02	0.9581	0.0419	0.7766	1.6522

ALCOHOL_FREQUENCY_T7	1.47	1.21	0.6781	0.3219	0.7667	1.6627
ALCOHOL_UNITS_T7	1.57	1.25	0.6381	0.3619	0.7109	1.7268
ALCOHOL_6UNITS_T7	1.28	1.13	0.7800	0.2200	0.6124	1.8605
SMOKE_DAILY_T7	1.04	1.02	0.9654	0.0346	0.4376	2.2010
CROHNS_COLITIS_T7	1.01	1.01	0.9870	0.0130	0.2825	2.7394
Mean VIF	**1.22**			**Condition Number**		**2.7394**

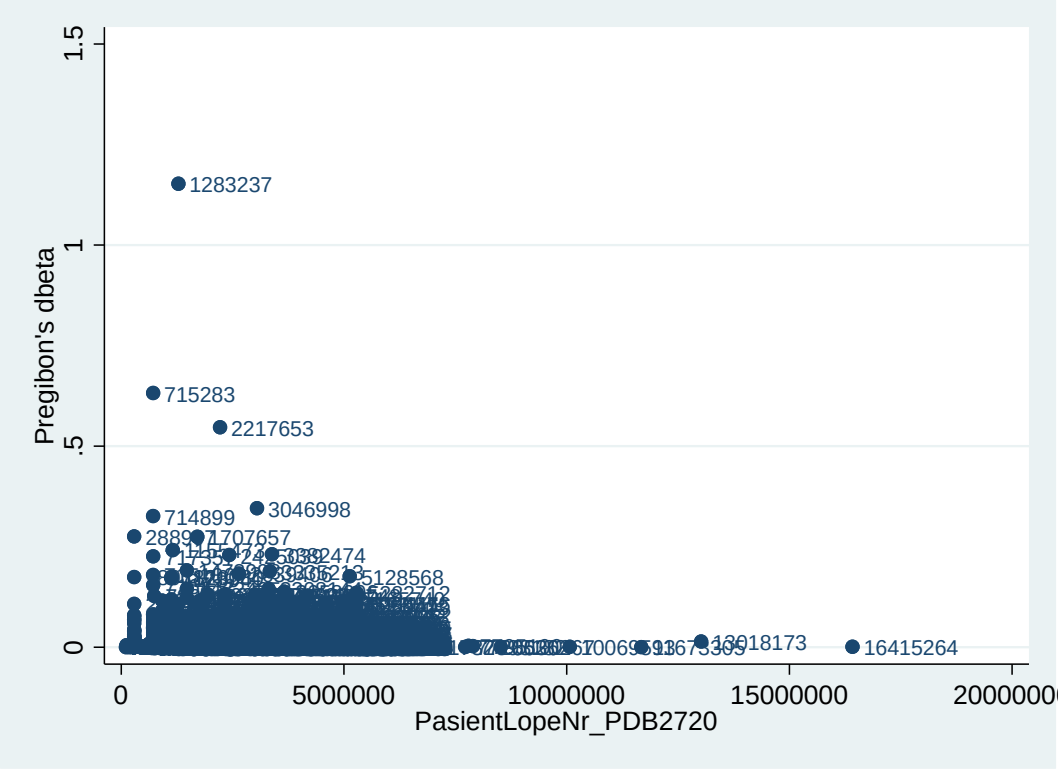
Multicollinearity occurs when two or more independent variables in the model are highly correlated. Two commonly used measures are tolerance (an indicator of how much collinearity that a regression analysis can tolerate) and VIF (variance inflation factor, an indicator of how much of the inflation of the standard error could be caused by collinearity) (70). If a variable is closely related to another variable(s), the tolerance goes to 0, and the VIF gets very large. There are no formal cut-off values for tolerance and VIF, however the usual ones seem to be VIF>10 and tolerance<0.2 (71,72). According to Table 4, we can see that the largest VIF (2.05 and 2.07) and lowest tolerance (0.4879 and 0.4827) belongs to antidiabetics (total_ddd_A10) and diabetes mellitus (DIABETES_T7), which makes sense as antidiabetics is a medication used to treat diabetes mellitus. Since the VIF<10 and tolerance >0.2, there exists no multicollinearity in the model. Another logistic regression analysis was completed, excluding the diabetes mellitus variable resulting in the p-value of antidiabetics to be >0.05.



Pearson residual against predicted values plot



Pearson residual against Pregibon leverage plot



Pregibon's dbeta plot

Graphs mentioned are used to detect influential observations that might have a significant impact on the model. Influential observations differ from all the other ones by being far away on the plots. By looking at the graph with Pearson residual plotted against predicted value, some observations such as patient id 1283237 differ from others by having a big Pearson residual value, but the following graph with shows that the leverage value of that patient is low and therefore won't have a big impact on the model if removed. Patient id 1707657 has a high leverage value, but when compared the logistic regression with and without the observation, no severe impact on the model were observed. All the patient ids that differed from all the others were excluded to assess their impact on the new logistic regression model, however no impact was observed such as a change of significant values to non-significant and vice versa.

Diagnostics for daily dosage and *K. pneumoniae* carriage

Hosmer-Lemeshow's goodness of fit test

Number of observations = 2684
Number of groups = 10
Hosmer-Lemeshow chi2(8) = 11.93
Prob > chi = 0.1541

Group	Probability	Observed 1	Expected 1	Observed 0	Expected 0	Total
1	0.1071	18	24.3	255	248.7	273
2	0.1252	40	31.3	227	235.7	267
3	0.1366	40	37.1	242	244.9	282
4	0.1464	43	35.7	209	216.3	252
5	0.1549	34	40.4	234	227.6	268
6	0.1628	42	42.7	227	226.3	269
7	0.1739	34	45.1	234	222.9	268
8	0.1893	46	48.7	223	220.3	269
9	0.2257	59	54.9	209	213.1	268
10	0.6280	81	76.7	187	191.3	268

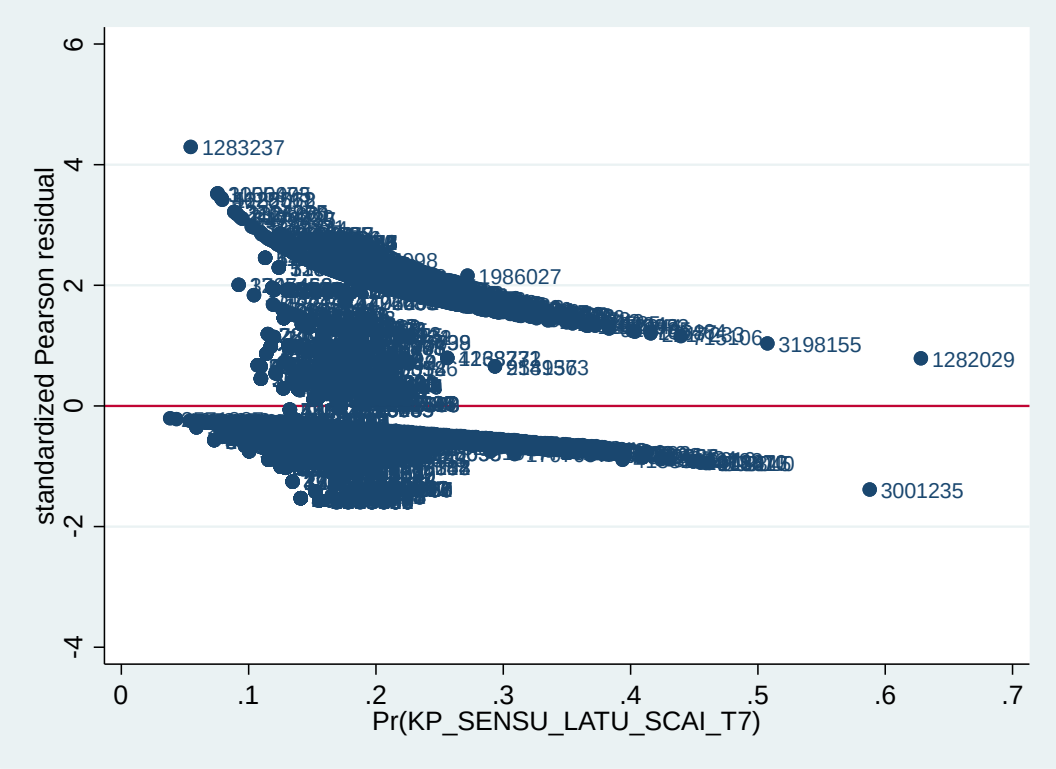
Hosmer-Lemeshoe's goodness of fit test shows that the p-value >0.05 which shows that there are no significant difference between expected and observed and therefore not a concern for our model.

Collinearity diagnostics

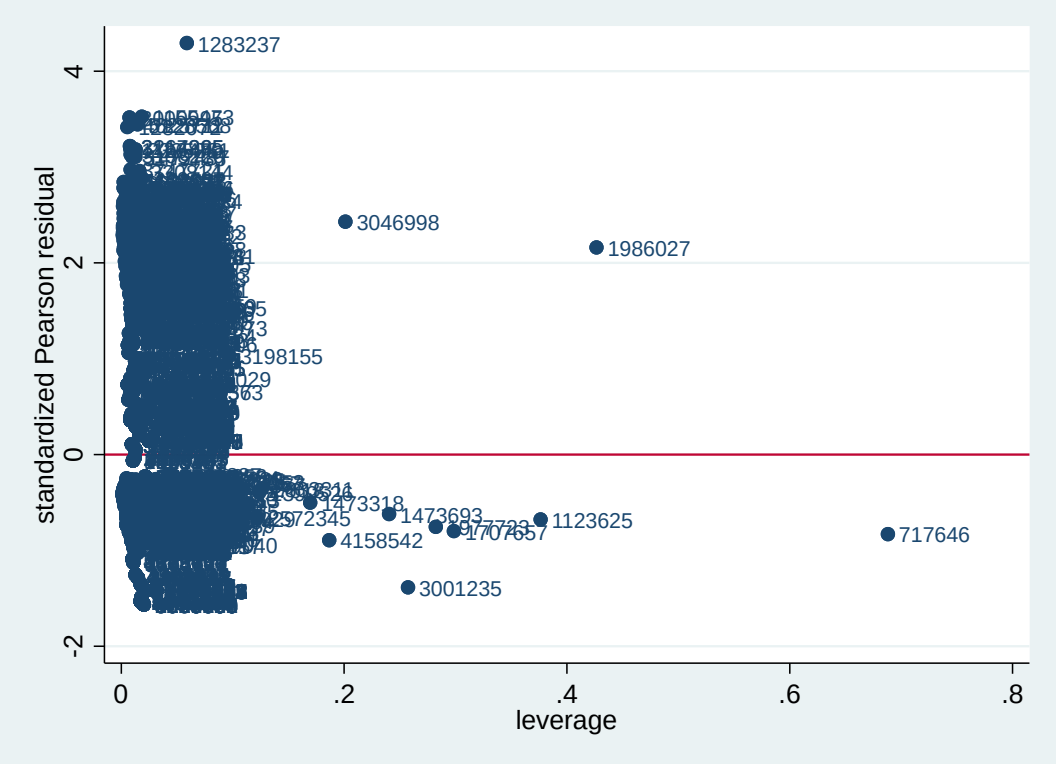
Variable	VIF	SQRT VIF	Tolerance	R-Squared	Eigenval	Cond Index
daily_dosage_A02	1.04	1.02	0.9642	0.0358	2.0553	1.0000
daily_dosage_A10	1.49	1.22	0.6727	0.3273	1.6025	1.1325
daily_dosage_C10	1.06	1.03	0.9413	0.0587	1.4433	1.1933
daily_dosage_H03	1.01	1.00	0.9949	0.0051	1.2041	1.3065
daily_dosage_J01	1.04	1.02	0.9656	0.0344	1.1139	1.3583
daily_dosage_M01	1.07	1.03	0.9349	0.0651	1.0976	1.3684
daily_dosage_N02	1.11	1.05	0.9011	0.0989	1.0850	1.3763
daily_dosage_N05	1.06	1.03	0.9474	0.0526	1.0105	1.4262
daily_dosage_N06	1.03	1.01	0.9722	0.0278	0.9838	1.4454
daily_dosage_P01	1.02	1.01	0.9833	0.0167	0.9552	1.4668
AGE_T7	1.14	1.07	0.8738	0.1262	0.9144	1.4993
DIABETES_T7	1.52	1.23	0.6591	0.3409	0.8735	1.5339
BRONCHITIS_T7	1.03	1.02	0.9704	0.0296	0.8593	1.5466
HOSPITAL_ADMISSION_TIMES_T7	1.04	1.02	0.9623	0.0377	0.8546	1.5508
ALCOHOL_FREQUENCY_T7	1.47	1.21	0.6781	0.3219	0.7757	1.6278
ALCOHOL_UNITS_T7	1.57	1.25	0.6381	0.3619	0.7017	1.7114

ALCOHOL_6UNITS_T7	1.28	1.13	0.7783	0.2217	0.6116	1.8331
SMOKE_DAILY_T7	1.03	1.01	0.9708	0.0292	0.4438	2.1519
CROHNS_COLITIS_T7	1.01	1.01	0.9889	0.0111	0.4141	2.2277
Mean VIF	**1.16**			**Condition Number**		**2.2277**

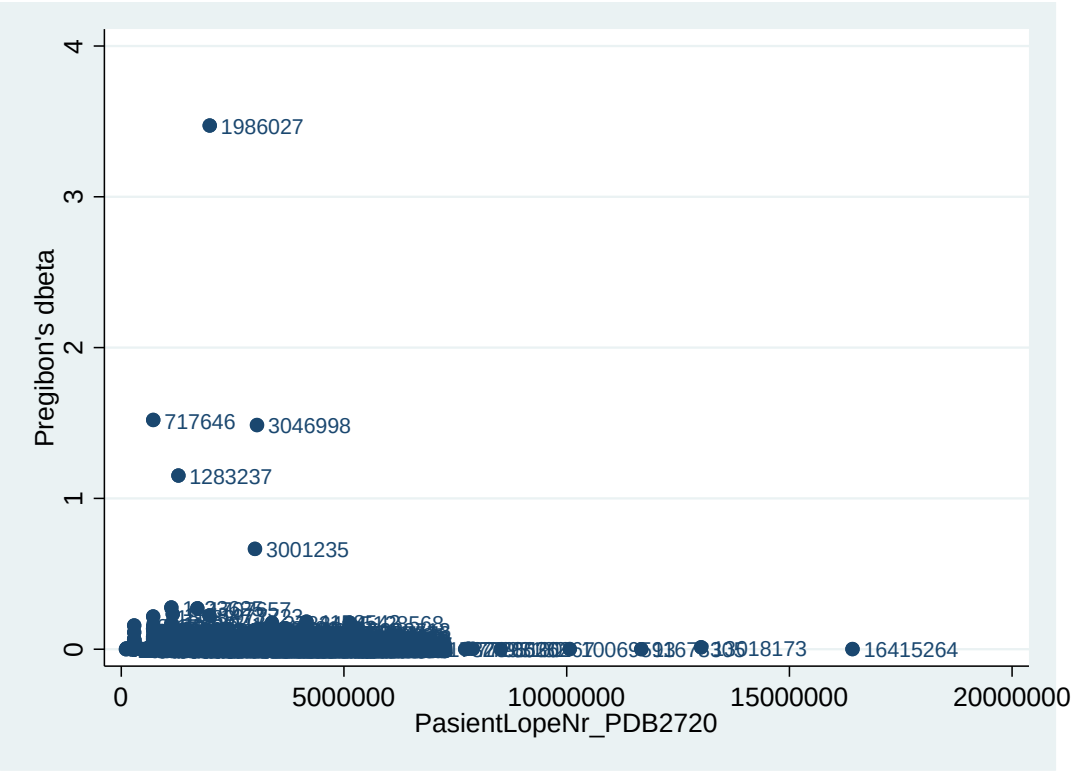
Collinearity diagnostics show that the largest VIF of 1.57 and lowest tolerance value of 0.6381 belongs to the alcohol units/occasion variable (ALCOHOL_UNITS_T7). The VIF and tolerance values are not a big concern for any indications of multicollinearity.



Pearson residual against predicted values plot



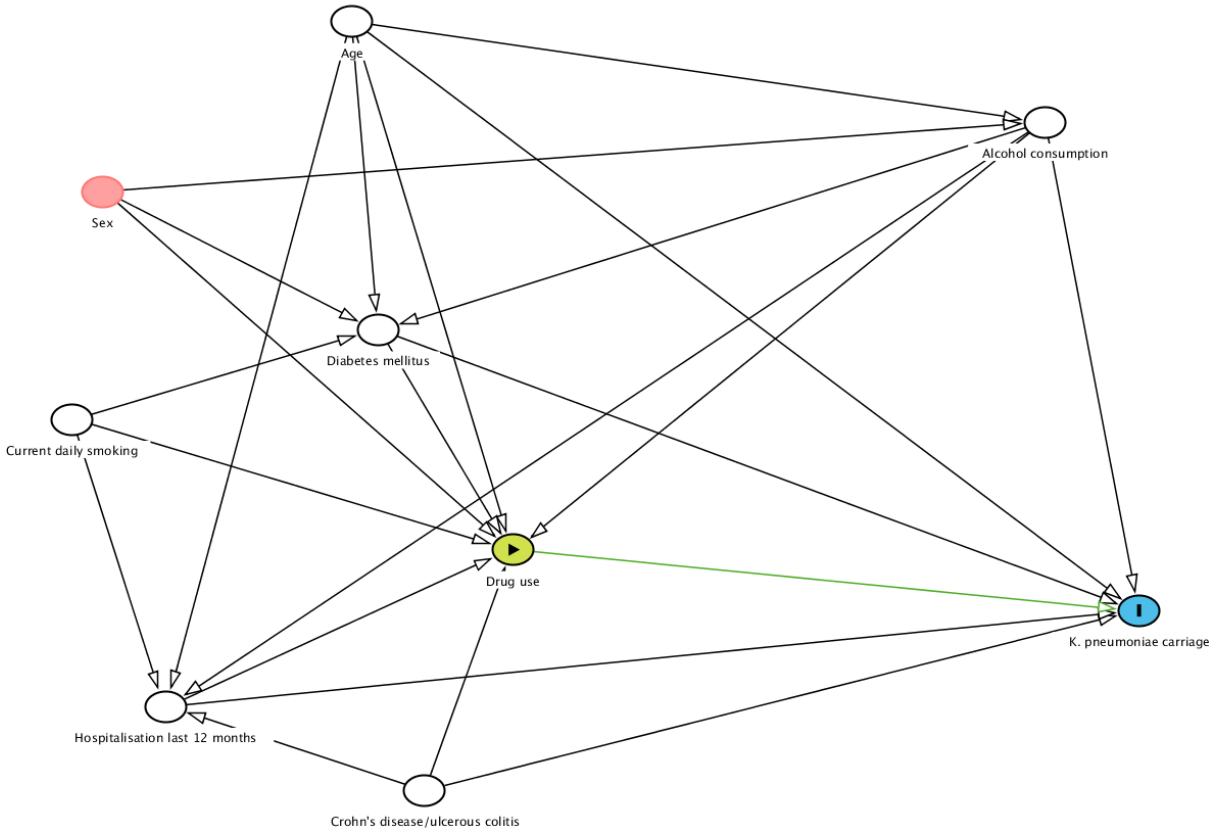
Pearson residual against Pregibon leverage plot.



Pregibon's dbeta plot

Patient id 1986027 had a high Pregibon's dbeta value, but when excluded in the logistic regression analysis, no impacts were observed. Patient id 717646 was also excluded and resulted in the same.

Appendix 5: Directed acyclic graph (DAG)



Illustrated using DAGitty. All white circles are being adjusted for with drug use an exposure and K. pneumoniae as outcome (73).

Appendix 6: Frequency of drug users for the past 6 months for non-antibiotic and 2 months for antibiotic before fecal sample

Drug user defined as having dispensed a drug for the past 6 months for non-antibiotic and 2 months for antibiotic before fecal sample

Drug groups and actives substances	ATC	Frequency	Percent
Antacid (A02)		**394**	**100**
Pantoprazole	A02BC02	189	47.97
Esomeprazole	A02BC05	102	25.89
Lansoprazole	A02BC03	50	12.69
Ranitidine	A02BA02	31	7.87
Omeprazole	A02BC01	16	4.06
Antacids with sodium bicarbonate	A02AH	6	1.52
Antidiabetics (A10)		**229**	**100**
Metformin	A10BA02	109	47.60
Insulin (human)	A10AC01	25	10.92
Glimepiride	A10BB12	22	9.61
Insulin glargine	A10AE04	14	6.11
Insulin aspart	A10AB05	11	4.80
Linagliptin	A10BH05	9	3.93
Sitagliptin	A10BH01	8	3.49
Insulin lispro	A10AB04	6	2.62
Liraglutide	A10BJ02	6	2.62
Insulin aspart	A10AD05	5	2.18
Saxagliptin	A10BH03	4	1.75
Metformin and sitagliptin	A10BD07	2	0.87
Dapagliflozin	A10BK01	2	0.87
Insulin (human)	A10AB01	1	0.44
Insulin glulisine	A10AB06	1	0.44
Glibenclamide	A10BB01	1	0.44
Metformin and vildagliptin	A10BD08	1	0.44
Vildagliptin	A10BH02	1	0.44
Exenatide	A10BJ01	1	0.44
Lipid-modifying drugs (C10)		**716**	**100**
Simvastatin	C10AA01	361	50.42
Atorvastatin	C10AA05	270	37.71
Pravastatin	C10AA03	30	4.19
Ezetimibe	C10AX09	23	3.21
Rosuvastatin	C10AA07	17	2.37
Fluvastatin	C10AA04	6	0.84
Red yeast rice (a natural medicine)	C10	3	0.42
Omega-3-triglycerides incl. other esters and acids	C10AX06	3	0.42
Simvastatin and ezetimibe	C10BA02	2	0.28

Lovastatin	C10AA02	1	0.14
Thyroid drugs (H03)		**265**	**100**
Levothyroxine sodium	H03AA01	262	98.87
Liothyronine sodium	H03AA02	2	0.75
Thyroid gland preparations	H03AA05	1	0.38
Antibiotics (J01)		**221**	**100**
Phenoxymethylpenicillin	J01CE02	45	20.36
Pivmecillinam	J01CA08	38	17.19
Doxycycline	J01AA02	20	9.05
Amoxicillin	J01CA04	20	9.05
Methenamine	J01XX05	15	6.79
Sulfamethoxazole/trimethoprim	J01EE01	14	6.33
Nitrufurantoin	J01XE01	14	6.33
Trimethoprim	J01EA01	11	4.98
Erythromycin	J01FA01	11	4.98
Ciprofloxacin	J01MA02	8	3.62
Clindamycin	J01FF01	7	3.17
Dicloxacillin	J01CF01	6	2.71
Clarithromycin	J01FA09	5	2.26
Azithromycin	J01FA10	3	1.36
Tetracycline	J01AA07	2	0.90
Lymecycline	J01AA04	1	0.45
Cefotaxime	J01DD01	1	0.45
Anti-inflammatory/antirheumatic drugs (M01)		**483**	**100**
Diclofenac	M01AB05	112	23.19
Ibuprofen	M01AE01	110	22.77
Naproxen and esomeprazole	M01AE52	82	16.98
Glucosamine	M01AX05	70	14.49
Naproxen	M01AE02	53	10.97
Etoricoxib	M01AH05	23	4.76
Piroxicam	M01AC01	18	3.73
Diclofenac, combinations	M01AB55	6	1.24
Celecoxib	M01AH01	4	0.83
Ketoprofen	M01AE03	3	0.62
Meloxicam	M01AC06	2	0.41
Analgesics (N02)		**504**	**100**
Paracetamol	N02BE01	190	37.70
Codeine and paracetamol	N02AJ06	149	29.56
Tramadol	N02AX02	78	15.48
Sumatriptan	N02CC01	25	4.96
Rizatriptan	N02CC04	14	2.78
Tramadol and paracetamol	N02AJ13	8	1.59

Zolmitriptan	N02CC03	8	1.59
Clonidine	N02CX02	6	1.19
Buprenorphine	N02AE01	5	0.99
Eletriptan	N02CC06	5	0.99
Oxycodone	N02AA05	4	0.79
Morphine	N02AA01	3	0.60
Fentanyl	N02AB03	3	0.60
Naratriptan	N02CC02	2	0.40
Almotriptan	N02CC05	2	0.40
Oxycodone and naloxone	N02AA55	1	0.20
Acetylsalicylic acid	N02BA01	1	0.20
Psycholeptics (N05)		**410**	**100**
Zopiclone	N05CF01	177	43.17
Diazepam	N05BA01	63	15.37
Melatonin	N05CH01	42	10.24
Oxazepam	N05BA04	41	10.00
Zolpidem	N05CF02	40	9.76
Prochlorperazine	N05AB04	13	3.17
Hydroxyzine	N05BB01	10	2.44
Nitrazepam	N05CD02	6	1.46
Levomepromazine	N05AA02	3	0.73
Chlorprothixene	N05AF03	3	0.73
Quetiapine	N05AH04	2	0.49
Lithium	N05AN01	2	0.49
Aripiprazole	N05AX12	2	0.49
Chlorpromazine	N05AA01	1	0.24
Clozapine	N05AH02	1	0.24
Olanzapine	N05AH03	1	0.24
Risperidone	N05AX08	1	0.24
Alprazolam	N05BA12	1	0.24
Chlomethiazole	N05CM02	1	0.24
Psychoanaleptics (N06)		**105**	**100**
Escitalopram	N06AB10	26	24.76
Amitriptyline	N06AA09	23	21.90
Mianserin	N06AX03	8	7.62
Mirtazapine	N06AX11	8	7.62
Paroxetine	N06AB05	7	6.67
Venlafaxine	N06AX16	7	6.67
Sertraline	N06AB06	5	4.76
Donepezil	N06DA02	5	4.76
Bupropion	N06AX12	4	3.81
Trimipramine	N06AA06	3	2.86
Citalopram	N06AB04	3	2.86

Chlomipramine	N06AA04	2	1.90
Nortriptyline	N06AA10	2	1.90
Doxepin	N06AA12	1	0.95
Rivastigmine	N06DA03	1	0.95
Antibiotics (P01)		**5**	**100**
Metronidazole	P01AB01	5	100

Appendix 7: Frequency of drug users before fecal sample

Drug user defined as having dispensed a drug before the fecal sample.

Drug groups and active substances	ATC	Frequency	Percent
Antacida (A02)		**659**	**100**
Pantoprazole	A02BC02	312	47.34
Esomeprazole	A02BC05	180	27.31
Lansoprazole	A02BC03	68	10.32
Ranitidine	A02BA02	64	9.71
Omeprazole	A02BC01	21	3.19
Antacids with sodium bicarbonate	A02AH	8	1.21
Alginic acid	A02BX13	4	0.61
Famotidine	A02BA03	2	0.30
Antidiabetics (A10)		**263**	**100**
Metformin	A10BA02	120	45.63
Insulin (human)	A10AC01	30	11.41
Glimepiride	A10BB12	26	9.89
Insulin glargine	A10AE04	18	6.84
Insulin aspart	A10AB05	14	5.32
Linagliptin	A10BH05	11	4.18
Insulin lispro	A10AB04	8	3.04
Sitagliptin	A10BH01	8	3.04
Liraglutide	A10BJ02	7	2.66
Insulin aspart	A10AD05	5	1.90
Saxagliptin	A10BH03	4	1.52
Dapagliflozin	A10BK01	3	1.14
Metformin and sitagliptin	A10BD07	2	0.76
Insulin (human)	A10AB01	1	0.38
Insulin glulisine	A10AB06	1	0.38
Glibenclamide	A10BB01	1	0.38
Metformin and vildagliptin	A10BD08	1	0.38
Metformin and linagliptin	A10BD11	1	0.38
Vildagliptin	A10BH02	1	0.38
Exenatide	A10BJ01	1	0.38
Lipid-modifying drugs (C10)		**869**	**100**
Simvastatin	C10AA01	433	49.83
Atorvastatin	C10AA05	324	37.28
Pravastatin	C10AA03	39	4.49
Ezetimibe	C10AX09	24	2.76
Rosuvastatin	C10AA07	22	2.53
Fluvastatin	C10AA04	10	1.15
Red yeast rice (a natural medicine)	C10	6	0.69

Simvastatin and ezetimibe	C10BA02	4	0.46
Omega-3-triglycerides incl. other esters and acids	C10AX06	3	0.35
Lovastatin	C10AA02	2	0.23
Colestipol	C10AC02	2	0.23
Thyroid drugs (H03)		**279**	**100**
Levothyroxine sodium	H03AA01	275	98.57
Liothyronine sodium	H03AA02	3	1.08
Thyroid gland preparations	H03AA05	1	0.36
Antibiotics (J01)		**1,562**	**100**
Phenoxymethylpenicillin	J01CE02	306	19.59
Pivmecillinam	J01CA08	245	15.69
Doxycycline	J01AA02	188	12.04
Amoxicillin	J01CA04	128	8.19
Sulfamethoxazole/trimethoprim	J01EE01	99	6.34
Trimethoprim	J01EA01	98	6.27
Erythromycin	J01FA01	82	5.25
Nitrufurantoin	J01XE01	64	4.10
Dicloxacillin	J01CF01	63	4.03
Ciprofloxacin	J01MA02	62	3.97
Clindamycin	J01FF01	61	3.91
Clarithromycin	J01FA09	50	3.20
Methenamine	J01XX05	42	2.69
Azithromycin	J01FA10	40	2.56
Tetracycline	J01AA07	12	0.77
Cefalexin	J01DB01	8	0.51
Lymecycline	J01AA04	7	0.45
Cefotaxime	J01DD01	4	0.26
Cloxacillin	J01CF02	2	0.13
Oflocaxin	J01MA01	1	0.06
Anti-inflammatory/antirheumatic drugs (M01)		**1,141**	**100**
Diclofenac	M01AB05	328	28.75
Ibuprofen	M01AE01	250	21.91
Naproxen and esomeprazole	M01AE52	162	14.20
Naproxen	M01AE02	124	10.87
Glucosamine	M01AX05	111	9.73
Etoricoxib	M01AH05	64	5.61
Piroxicam	M01AC01	52	4.56
Diclofenac, combinations	M01AB55	25	2.19
Ketoprofen	M01AE03	12	1.05
Celecoxib	M01AH01	7	0.61
Nabumetone	M01AX01	3	0.26
Meloxicam	M01AC06	2	0.18

Indometacin	M01AB01	1	0.09
Analgesics (N02)		**1,142**	**100**
Paracetamol	N02BE01	420	36.78
Codeine and paracetamol	N02AJ06	364	31.87
Tramadol	N02AX02	220	19.26
Sumatriptan	N02CC01	37	3.24
Rizatriptan	N02CC04	22	1.93
Zolmitriptan	N02CC03	15	1.31
Tramadol and paracetamol	N02AJ13	12	1.05
Oxycodone	N02AA05	10	0.88
Eletriptan	N02CC06	10	0.88
Buprenorphine	N02AE01	8	0.70
Clonidine	N02CX02	6	0.53
Morphine	N02AA01	4	0.35
Fentanyl	N02AB03	4	0.35
Naratriptan	N02CC02	3	0.26
Oxycodone and naloxone	N02AA55	2	0.18
Acetylsalicylic acid	N02BA01	2	0.18
Almotriptan	N02CC05	2	0.18
Ketobemidone	N02AB01	1	0.09
Psycholeptics (N05)		**706**	**100**
Zopiclone	N05CF01	266	37.68
Diazepam	N05BA01	109	15.44
Melatonin	N05CH01	87	12.32
Oxazepam	N05BA04	79	11.19
Zolpidem	N05CF02	73	10.34
Hydroxyzine	N05BB01	32	4.53
Prochlorperazine	N05AB04	21	2.97
Nitrazepam	N05CD02	15	2.12
Levomepromazine	N05AA02	6	0.85
Chlorprothixene	N05AF03	3	0.42
Alprazolam	N05BA12	3	0.42
Olanzapine	N05AH03	2	0.28
Quetiapine	N05AH04	2	0.28
Lithium	N05AN01	2	0.28
Aripiprazole	N05AX12	2	0.28
Chlorpromazine	N05AA01	1	0.14
Clozapine	N05AH02	1	0.14
Risperidone	N05AX08	1	0.14
Chlomethiazole	N05CM02	1	0.14
Psychoanaleptics (N06)		**163**	**100**
Amitriptyline	N06AA09	48	29.45
Escitalopram	N06AB10	41	25.15

Mirtazapine	N06AX11	15	9.20
Mianserin	N06AX03	12	7.36
Venlafaxine	N06AX16	9	5.52
Paroxetine	N06AB05	7	4.29
Sertraline	N06AB06	6	3.68
Donepezil	N06DA02	6	3.68
Trimipramine	N06AA06	4	2.45
Citalopram	N06AB04	4	2.45
Bupropion	N06AX12	4	2.45
Chlomipramine	N06AA04	2	1.23
Nortriptyline	N06AA10	2	1.23
Doxepin	N06AA12	1	0.61
Caffeine	N06BC01	1	0.61
Rivastigmine	N06DA03	1	0.61
Antibiotics (P01)		**86**	**100**
Metronidazole	P01AB01	86	100