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Use of group based trajectory modelling to identify groups based on trajectories obtained for overall number of antibiotics prescription to children age 0-3 years in Norway during year 2004 to 2017.

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Abstract

Background

Bacterial infection occur frequently in children. In 2015 more than 900,000 children below 5 years were killed due to respiratory tract infections (RTIs). Early life onset and prolonged use of antibiotics in children can leads to health complications later in life. Antibiotics prescribing in young children is affected by many factors and identifying these factors can provide an opportunity to develop strategies for better prescribing.

The Norwegian government plans to reduce consumption of antibiotics agents with 30% by 2020 compared to the level in 2012.

Purpose

The purpose of this study was to identify groups of children based on the trajectories obtained by total number of prescriptions collected during first three years of life using GBTM.

Material and methods

Data on redeemed antibiotic prescriptions was obtained from NorPD for all children 0-3 years born in Norway from 2004 to 2017. Those without a personal identifier number and less than two prescriptions were excluded. Group-based trajectory modeling is used to identify clusters of children that are following similar trajectories of a single indicator of interest like gender or birth season.

Results

A total of 184012 children were included. Trajectory models with four groups was considered best fit for our study based on the criteria of model selection in GBTM. Group 1 had 1.8% of children from population of 184012, in that the proportion of children with antibiotic

prescription was approximately 48%, group 2 had 39.7% of children in this the proportion of children with the antibiotic prescription was around 17%, group 3 had highest number of children 57.8% in that the proportion of children with antibiotic prescription was around 19%, group 4 consisted of lowest number of children 0.73% in it the proportion of antibiotic prescription was 58%. The average number of prescription in groups (1, 2, 3, and 4) were 9.97/child, 2.74/child, 2.70/child and 12.01/child respectively. The trajectories obtained as per birth season showed that the first peak in group with highest proportion of antibiotic prescriptions (red color curve) occurs around the first winter experience of children. There was no association between birth seasons and proportion of children collecting antibiotic prescription as per the trajectories obtained for the complete database, based on the descriptive table shown in results section. The trajectories based on gender for male and female were identical, and even the group sizes were approximately same for both genders.

Conclusions

Our results do not suggest marked differences among children born in birth seasons and the association to the trajectories showing proportion of antibiotics prescription collected. There was considerable difference in the group sizes and proportion of children in the trajectories obtained for prescription based by birth season. However, winter was the duration when collection of antibiotics prescription was highest among children.

Abbreviations

AIC	Akaike information criterion
AMR	Antimicrobial resistance
AOM	Acute otitis media
BIC	Bayesian information criterion
DDD	Defined daily dose
FHI	Folkehelseinstituttet
FOR	Fear of recurrence
GBTM	Group based trajectory modelling
GP	General Practitioner
NorPD	Norwegian prescription database
PCV	Pneumococcal conjugate vaccine
PDC	Proportion of days covered
RTI	Respiratory tract infection
UTI	Urinary tract infection
WHO	World Health Organization

1 Background

1.1 Antibiotics and Children

The public health strain of infectious diseases in childhood is vast. Children younger in age have higher chances to pick up infections due to tender immune system, and narrower passages (in sinus, bronchi and ear) . The other factors for high rate of infection transmission in childhood are close physical contact, and minimal use of sneezing / coughing behavior. In Norway, the first line of healthcare services are provided by general practitioners (GPs) for all citizens (1).

Worldwide RTIs from bacteria are major cause of mortality and morbidity. In 2015 more than 900,000 children 5 years were killed due to pneumonia. These numbers accounted for 16% of all deaths in that age group. Consumption of antibiotics shows cyclic variations, and in the Northern hemisphere, the number of users is normally highest during the winter months (2). Airway infections is the most frequent indication for treatment, and the one-year periodic prevalence of use is highest among children 0-3 years (3).

In children 20-50% of the antibiotic prescriptions are given to treat nonbacterial upper respiratory tract infections, for that antibiotics are mostly ineffective. A study from Denmark shows that exposure to antibiotics differs significantly between children born in different seasons and age at first use of antibiotics (4).

Further, children cannot be treated as a single homogenous group. There are major differences among neonates, infants, children and adolescents in respect to pharmacodynamics and pharmacokinetics. The efficacy and safety of medicine in children is primarily derived from clinical trials for adults (5).

Approximately one-third of outpatient medication prescription provided to children are either off-label or unapproved by monitoring authorities. Children given untested medicine might experience harm. As per documented pediatric adverse conditions for drugs used off label comprised chloramphenicol induced gray baby syndrome and propofol sedation related with cardiac failure and deadly metabolic acidosis (6).

The AMR and emergence of multi-resistant bacterial strains is of clinical concern with major implications to public health worldwide. Several studies have highlighted increase in antibiotic resistance by bacterial pathogens to cause infections globally (7). There are differences in antibiotic use across the world based on local medication practices, availability of antibiotics without prescription, and where regulations of antibiotic usages are limited. In some countries with few resources, the antibiotic consumption would be less due to the drug shortage (8).

A study in UK in pediatric centers found that changes in antibiotic prescription are not solely dependent on patients related factors. Newly qualified GPs from UK prescribe antibiotics less often than older GPs, also GPs with higher workload prescribe more antibiotics. The prescribers are influenced by social norms. Children, aged persons, smokers, females and people with multiple comorbidities possess higher risk of complications due to infections and are prescribed antibiotics frequently (9).

As per a German study delayed antibiotic prescription, particularly waiting and observing is a good way for avoiding antibiotics especially in acute otitis media AOM (age > 24 months) and sinusitis. A delayed antibiotic prescription can be implemented in two ways (10).

1. Wait and observe. The child is observed carefully by parents, a medical checkup or telephonic consultation is required. If the child's condition does not improve or worsens, then the antibiotics be prescribed after 48 hrs.

2. Give a prescription that can only be redeemed if there is no improvement. However, there is a risk that parents may hoard the antibiotics, take it themselves or give it to their child without a further visit to the doctor (10).

Interventions to improve prescribing of antibiotics aims for usage of narrower spectrum of antibiotics instead of broad spectrum antibiotics and decrease inappropriate antibiotics prescribing. Interventions can be directed at general public, patients, physicians or combinations of these groups (11).

1.2 Epidemiology of RTIs and UTIs

Respiratory tract infections include colds (rhino pharyngitis), (AOM), laryngitis, bronchitis and pneumonia. However, AOM and pneumonia could have bacterial etiology (12). AOM is a widely occurring disease in early infancy and childhood. Approximately 10% of children have an issue of AOM by 3 months and by age of 3 years around 50-85% of children experience one episode of AOM. The peak age-specific incidence occurs in 6-15 months of age. Despite several clinical trials, there is no agreement for optimal therapy of AOM. The proportion of patients receiving antibiotics treatment for AOM vary from 56% in Netherland to 95% in USA, Australia and Canada. For many years delayed antibiotic strategy for AOM has been encouraged (13).

A Norwegian study covering 24,888 consultations on 19,938 patients during December 2004 to November 2005 examined data on RTIs in children 0-6 years. RTI was common among 2-3 years children, and the majority of diagnosis were of AOM, cough and upper respiratory tract infection. Antibiotics were prescribed in 26.2 % of the consultations (14). RTIs are monitored through *Sykdompulsen*, a registry of infectious diseases it is updated monthly for the number of consultations with GPs and emergency services. Consultations show seasonal variation for RTIs. The number of consultations is lower during holidays and public holidays. This is particular around Christmas / New Year and Easter and during the summer holiday weeks (15).

UTIs are common bacterial infections in children below 2 years. Well-treated UTIs have overall a good outcome. However, delayed treatment can lead to renal scarring (16). Cumulative incidence of UTIs in children before the age of two years is 2.1% for girls and 2.2% for boys. Girls reach a higher rate of incidence compared to boys between 3-6 months of age (17).

As per a study in USA the recurrence rate for UTI in girls is significant despite the absence or presence of a urinary tract abnormality. Recurrence rate for UTI in males is less frequent, it affects approximately one third of those with UTI (18). Oral antibiotic treatment is preferred as the first choice for urinary tract infections in children both in abroad and Norway (19).

1.3 Antibiotics Prescriptions in Norwegian Children

The Norwegian Prescription database (NorPD) has been available since 2004. As per an article published in 2019, there is 11% reduction in consumption of antibiotics measured as DDD compared to 2012 (20). Five of the 20 most commonly delivered drugs to the age group 0-17 years were antibiotics (21).

In Norway in 2017, there were about 800,000 consultations of children 0-5 years at GPs and in emergency departments. RTIs was diagnosed in 34% of these cases (22). Several studies confirm that the amount of antibiotics agents consumed is associated to the level of resistance of pathogenic bacteria (23-24). Although Norway has low levels of antimicrobial resistance (25), the government published a plan to reduce the consumption of antibiotics agents with 30% by 2020 compared to the level in 2012 (26).

Another prescription register study from Norway records the delivery of antibiotics in children < 18 years. The proportion of prescription for antibiotics in 2016 was highest in the age group < 3 years with 389/1 000, compared with 164/1 000 for children in the age group 6 - 11 years. In children < 3 years in 2016 there were 412 prescription/1 000 boys compared to 363 prescriptions/1 000 girls. From year 2005 to 2016 the number of prescriptions decreased by 28% for children < 3 years (27).

There are other reasons for reducing the consumption of antibiotics agents. There are gastrointestinal side effects like diarrhea and change in microbiota. A study in Finland found that use of antibiotics agents among children, especially macrolides, was associated with reduced diversity in microbiota (28). Broad-spectrum antibiotics change the properties of the microbiota, which is assumed to be function in the monitoring of the immune system (29).

The relationship of postnatal exposures to antibiotics in the first year of life with later development of allergic diseases in children have been reported in some studies from several countries .A recent study conducted in Japan, found that the antibiotic use in first two years of age was associated to dermatitis and rhinitis. The same study also highlighted that children who were given antibiotics early in life later had increased probability of asthma (30).

A study found that usage of antibiotics may enhance the probability of asthma by decreasing the defensive effect of microbial exposure. However, the confirmation of a relation between usage of antibiotics in children and development of asthma has been inconsistent (31). A study comparing the microbial profile between individuals with and without obesity found a lower distinctiveness of microbes in individuals with obesity. The first year of life is crucial for the development of the microbiome since the infant gut advances from sterile environment to a firm environment similar to adult gastrointestinal tract. There is incomplete recovery of microbiota after antibiotic treatment. These disturbances may lead to weight gain in future. There is small association between consumption of antibiotics in infancy (<24 months) and childhood overweight in few subgroups of children (32).

Another recent study in Denmark identified the association between birth seasons and delivery of antibiotics agents to children during the first year of life. The birth seasons were mapped as winter (December–February), spring (March-May), summer (June-August) and autumn (September-November). The probability of a first prescription enhanced with age throughout infancy and changed by season (4).

However, it is unknown whether arbitrary set dates is optimal when predicting time to first treatment or number of treatments during the first 3 years of life. Prescribing of antibiotics to children before the age of three is influenced by many factors. The mapping of these factors could be utilized to target interventions to reduce prescribing.

The Norwegian antibiotic prescription pattern from 2004 would had been effected by measures and events that occurred during the course of time like PKV, and mycoplasma epidemics (33), and seasonal influenza due to bacterial secondary infection (34). There are events that would reduce prescribing like introduction of PKV vaccination program. PKV had been the part of childhood vaccination program since 2006 (35).

There had been regular amendments in national guidelines for antibiotic usage in primary health care (36-38). Children born from 01.07.06 received the vaccine as the usual standard program, and those born from 01.01.06 had the option to obtain vaccination (39). As per a Norwegian cohort study that included children born in 2001-2008, the incidence of AOM and lower respiratory tract infections among children 12-36 months of age irrespective of vaccination status decreased by 1.5-2.5% for children born in 2008 compared with children born before 2006 (40).

There have been three major mycoplasma epidemics in Norway during 2006, 2011-12 and 2016-17. It is mapped through a voluntary cooperation between FHI and medical microbiological departments in Norway (33, 39). However, it should be noted that most often children 3-15 years are affected by mycoplasma pneumonia (33). In Norway seasonal flu normally occurs between weeks 40-20. FHI shows that children under the age of 12 might receive secondary or simultaneous infections with ear and pneumonia during this duration. In this scenario, a doctor might prescribe treatment with antibiotics (34).

The guidelines for pediatric treatment with antibiotics agents were first published in 2000 (36), were revised in October 2008 (27), then in November 2012 (37) and later in 2014-2015 (41). The major difference between the editions in 2000 and 2008 is stricter regulation for treatment of respiratory infections, and less frequent prescription for amoxicillin both for respiratory and urinary tract infections (27).

1.4 Method for investigating Antibiotics consumption pattern

In this project we use group based trajectory modeling to demonstrate differences in collection of antibiotic prescriptions and continuity across children 0-3 years. The purpose of using GBTM in our analysis is to better understand the time-varying antibiotic prescription patterns and ease the interpretation of results to identify hidden groups in trajectories.

Group based trajectory modelling (GBTM) had been applied in clinical and non-clinical settings, and was initially developed to study the developmental pattern of criminal behavior. GBTM is now used in biomedical research in varied segments as chronic kidney disease progression, obesity, pain, smoking, medication adoption and adherence, and concussion symptoms (42, 43).

In GBTM the trajectories from each group follow a unique response pattern. Initially the GBTM was meant to examine patterns of change over several years. The underlying groups identified by GBTM are not to be considered unique from one another, rather as a statistical approximation. There would be members in population that would clearly belong to a particular group while others would be tougher to classify (43).

The trajectories obtained should not be considered as exact trajectories that individuals follow during a study period. It should be used as tool for interpreting heterogeneity in a data set and good understanding of change and continuity with graphical presentation (44).

There are several measures to understand medication pattern (45), like Percentage of Days Covered (PDC). When antibiotic prescription patterns are to be estimated GBTM are superior to PDC. PDC limit the long term medication use to a single scalar, but GBTM accounts for varying patterns (46). This reduction in PDC makes time oriented changes in antibiotics prescription delivery difficult to interpret.

GBTM is based on statistical method called finite mixture modeling (47). This may enable us to characterize patterns of antibiotic prescription over time and identify the prescription collection differences based on e.g. gender and birth seasons. However, these procedures could even be applied in birth period and antimicrobial prescription for children.

For example, one study using GBTM was done among women recently diagnosed with gynecological cancers and fear of recurrence (FOR). FOR includes different types of fears related to illness like that cancer will progress, recur or metastasize. Several papers suggest that around 17-72% of cancer patients reported higher levels of FOR. High level of FOR remains in subgroup of cancer survivors even years after treatment is completed. Longitudinal studies can be used to describe changes in FOR over a period.

However, more can be learned by finding subgroup of women that follow similar pattern of change over period. Probably, women who begin with high FOR that decreases with time might differ in characteristics to women with initial low FOR and remain stable. These changes over time and predictors of these changes enable clinicians to target those who require intervention.

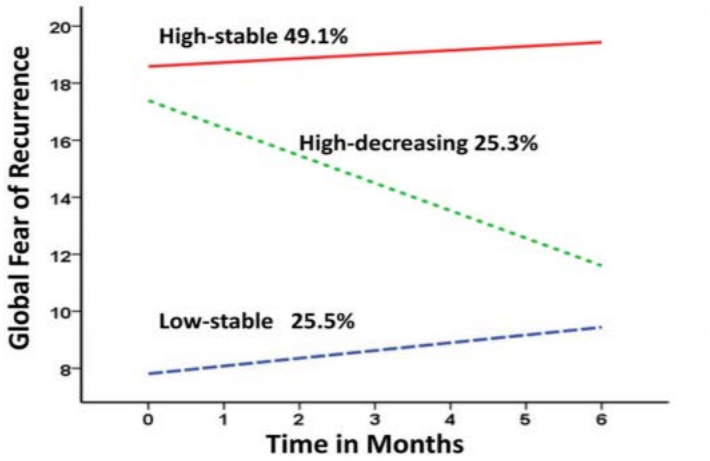

Figure 1.1. Trajectories of global fear (Source: Manne, S.L., Myers-Virtue, S., Kissane, D., Ozga, M.L., Kashy, D.A., Rubin, S.C., Rosenblum, N.G. and Heckman, C.J., 2017. Group-based trajectory modeling of fear of disease recurrence among women recently diagnosed with gynecological cancers)

The first subgroup low-stable comprised 25.5% had low global FOR at first assessment and remained low over time. The high-decreasing subgroup comprised 25.3% of the sample initially had high global FOR, but it decreased over time. The third subgroup high-stable was largest with 49.1% of the sample. The women in this subgroup maintained high global FOR throughout the time. Previous studies have suggested that woman with high-stable FOR are more prone to be diagnosed with metastatic cancer (48, 49).

Another study based on GBTM assessed adherence to antihypertensive medicines in adults in a pharmacy setting. Adherence to medication is the extent to that a patient consumes the medication as prescribed. Non-adherence is around 34-50% for chronic illness (50). Proportion of Days Covered (PDC) is one way to measure adherence in clinical settings. However, this results in loss of information especially on the pattern of adherence.

As per above study a patient who misses medication every alternate days would have similar PDC to patient who discontinues medication halfway in treatment. Patients that discontinue medication need different mediation compared to those that forget to take medication, each group needs to separate intervention strategy to ensure they abide to proper intake of

antihypertensive medication. GBTM was used to measure adherence to medication in this example of pharmacy dispensing records. GBTM identified groups of patients that followed similar pattern of pharmacy medication refill behavior in this example.

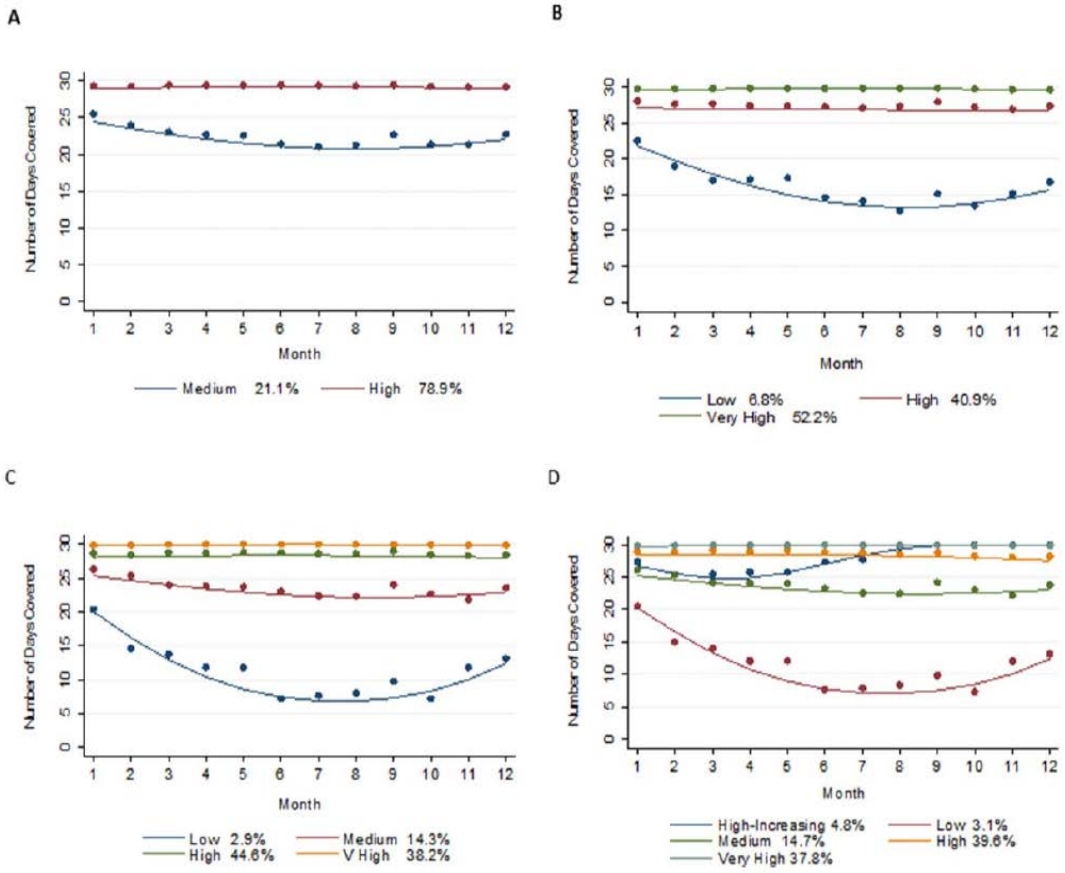

Figure 1.2 Trajectory Group Models with 2-5 groups (Source: Dillon, P., Stewart, D., Smith, S.M., Gallagher, P. and Cousins, G., 2018. Group-based trajectory models: assessing adherence to antihypertensive medication in older adults in a community pharmacy setting).

In figure 1.2 four models illustrate 2-5 adherence trajectory groups. The X-axis reflects 30 day interval in follow-up duration. The Y-axis reflects the number of days covered with antihypertensive medication during 30 days period. Adherence of 905 patients is shown for duration of 12 months using GBTM. The increase in number of groups provided better statistical fit BIC and AIC. The three-group model was considered best fit in this example as it fulfilled the requirement to have minimum group size of 5%.

The three group model illustrates three distinct trajectories, each trajectory reflects a pattern of medication adherence during a period of 12 months. The three groups are very high level of adherence 52.2 %, consistent high level 40.9% and low level of adherence 6.5% (50). The purpose of GBTM is to not find true number of trajectory groups. However, to find the distinct features in data (51). After 7-8 months the number of days covered with antihypertensive drugs in low level of adherence group drops from around 23 days to 13 days per month.

In GBTM the fundamental concept of interest is the distribution of outcomes conditional on age (or time); that is, the distribution of outcome trajectories denoted by $P(Y_i|Age_i)$, where the random vector Y_i represents child i's longitudinal sequence of collection of antibiotics prescription and the vector Age_i represents child i's age in months when each of those measurement is recorded. The group-based trajectory model assumes that the population distribution of trajectories arises from a finite mixture of unknown order J. The likelihood for each child i, conditional on the number of groups *J*, may be written as below (52).

$$P(Y_i|Age_i) = \sum_{j=1}^{J} \pi^j \cdot P\left(Y_i\middle|Age_i, j; \beta^j\right)$$

π^j is the probability of being in group j, and the conditional distribution of Y_i given membership in j is represented by the unknown parameter vector β^j that among other things determines the shape of the group-specific trajectory. The trajectory is modeled with up to a 5th order polynomial function of age (52).

Therefore, in GBTM individuals that follow a similar longitudinal progression of outcomes are identified and grouped together. GBTM assumes there are unrecognized subpopulation or separate groups based on their trajectory over time. Statistically, GBTM involves the concurrent

estimation of different regression models, linking the information from all models to identify the maximum probability of belonging to a potential trajectory group for the same individual (53).

Several factors need to be considered while analyzing studies that implemented GBTM. These are the duration of the study, the number of trajectory groups resulting from the analysis, the curves of trajectory groups identified and the drugs category studied. The number of trajectories in most of the studies are 4-6 adherence groups. However, a study by Lo-Ciganic et al., for hypoglycemic drugs classified adherence patients in patients using seven trajectory groups (54).

On the other hand, Greenley et al., found only two adherence trajectories for patients on thiorpurine in Inflammatory Bowel Disease (55). The main goal of GBTM is to describe and summarize different patterns, to ease the complexity of the situation and better understand differences between individual or patients behavior. Therefore, a key point is that the individual belonging to particular trajectory groups are similar in many aspects rather than being identical (56).

2. Objectives

The main objective of this study is to investigate whether it is possible to identify groups using GBTM based on the trajectories obtained for overall number of prescriptions in the first 3 year of life.

The secondary objective is to investigate if birth seasons give different trajectories.

2.1 Hypothesis

Our hypothesis assumes that it is possible to identify groups using GBTM to identify trajectories for total number of prescriptions given in children 0-3 years in Norway.

3. Material and Method

3.1 Data Material

Data on dispensation of systemic antibiotics during the period 2004-2017 for the 0-3 years age group is obtained from NorPD. NorPD contains information about the drug user, drug and prescriber. The database consists of retrospective longitudinal data and includes complete disclosure data for the study population. The complete description of NorPD is described elsewhere in Furu (57).

3.2 Method

3.2.1 Study Design

Descriptive analysis is done in a cross-sectional perspective while regression analysis is done in a cohort perspective.

3.2.2 Study Population

We included any children who collected more than or equal to 2 and less than or equal to 20 antibiotic prescriptions in first three years. The database is divided into two base groups. First group consist of data without a valid pseudo birth date, second group (database II) consist of data with a valid pseudo birth date. The following chart shows the second database group with inclusion and exclusion. In database II an exclusion has been made if there is no pseudo birth number, or lack of information about gender. Missing data are common in any study, especially if data is collected repeatedly over time. The collection of a complete dataset on individual is almost impossible. For example, in a cross-sectional survey the missing data is in form of individual non-response. Here the individual is not able or does not want to respond to a

particular question. Figure 3.1 shows the inclusion and exclusion of prescriptions that were not assigned any permanent ID, had less than 2 or more than 20 prescriptions, missing data. Then we combined all the prescriptions with their respective valid patient ID.

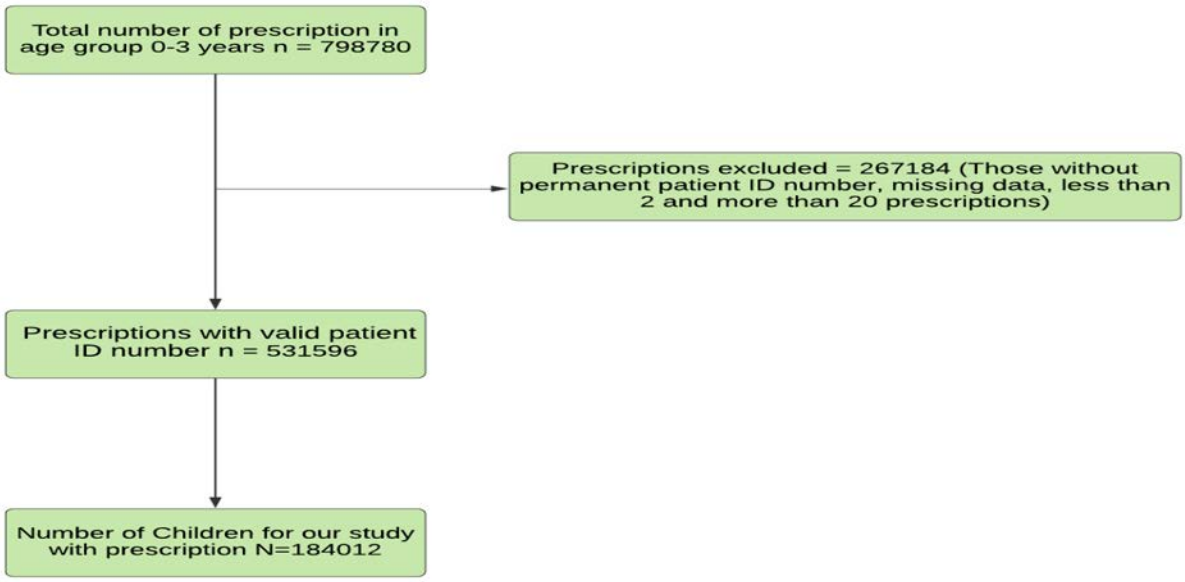

Figure 3.1 Flowchart for the inclusion and exclusion in the period 2004-2017.

3.2.3 Variables and definition

Prescription Delivery Year and month

It is used to calculate age and time to first delivery of antibiotics.

Patient ID Number

These allow to follow the individuals over time. In our study it would be used to calculate the number of prescriptions given to respective individual patient. Those children without pseudo birth ID number are given ID Key. It is not possible to use these random numbers to follow individuals over time. They would be excluded from our dataset for analysis.

Pseudo Birth Date

SPSS was used to generate pseudo birth date. The pseudo birth date was calculated as taking the 15th of every month as pseudo date for children born in that particular month. This gives the least margin of error. This is significant to calculate the approximate age and time to first prescription of antibiotics. In some cases where the date of birth is before 15th of that respective month and they have received antibiotics treatment in the same month before the date of 15th, that individual would have negative age. We did not include these children in our dataset.

Prescriptions

The number of prescriptions delivered is used as a measure of consumption. Children with similar ID numbers are summed up with their total prescriptions individually. Furthermore, we included children with more than or equal to two prescription and less than or equal to 20 prescriptions till the age of three years.

Birth Season

The four birth seasons would be considered for our analysis, they have been coded as 1,2,3,4 by using SPSS.

Seasons	**Months**	**SPSS Code**
Winter	December-February	1
Spring	March-May	2
Summer	June-August	3
Autumn	September-November	4

Table 3. 1 Birth Seasons with corresponding months and codes in SPSS.

Children born in the spring (March-May) would experience winter months at 8-10 months of

age. As per the pseudo birth date Children born on 15 May would be 9 months old on 15 February and children born on 15 April would be 8 months old on 15 December.

3.2.4 Software Used

The following software were used

1. IBM SPSS for removing variables from NorPD that were not relevant(dispensing date, patient without ID number, prescriber's year of birth, prescriber's sex, prescriber's profession code, prescriber without ID number, patient's residential county number, dispensing number, number of packages, prescription pharmacy retail price, number of DDD, prescription category, prescription category number, drug article number, drug brand name, drug package size, drug strength, drug package unit, DDD value, DDD unit). We used SPSS for dataset analysis, removing missing values, creating pseudo date of birth, calculating age.
2. Microsoft Excel was used to calculate average antibiotics prescription in children.
3. GBTM analysis are performed using Stata/MP 16.0 for Windows (StataCorp Revision 2019, College Station, Tx, USA)

The GBTM program a well-established SAS-based procedure for estimating group-based trajectory model. GBTM provides a statistical method to identify groups of separate trajectories that are summarized by a finite set of different polynomial functions of age or months as per maximum likelihood estimation (58, 59). The shape of individual trajectory is dependent on the order of polynomial function used for modeling. The order of polynomial should be high to match the shape that might emerge from data. This is significant to analyze cyclical patterns (56). This thesis uses cyclical pattern for analyzing antibiotic prescription collection during the seasons for first three years of life.

Installation of Traj can be done by using the following commands within Stata. An extra command, trajplot, supports plotting the results.

. net from http://www.andrew.cmu.edu/user/bjones/traj

. net install traj, replace

The datasets including variables of interest were transposed from long format to wide format in this thesis. Therefore, maximum likelihood estimators would offer unbiased and asymptotical parameter estimates.

3.2.5 Syntax

traj [if exp] , var(varlist) indep(varlist) model(string) order(numlist)

trajectory variables var (varlist) dependent variable, here are the prescriptions taken during 0-3 years of age.

Indep (varlist) independent variables, it is when the dependent variables measured.

Order(numlist) polynomial type ((0=intercept, 1=linear, 2=quadratic, 3=cubic)

3.2.6 Model Selection

The software provides three alternative specifications of p(.): the censored normal distribution also known as the Tobit model, the zero-inflated Poisson distribution, and the binary logit distribution.

The following commands fits our four-group model to the antibiotics collection data during a defined period and graphs the results.

traj, var(p1-p36) indep(t1-t36) model(logit) order(3 3 3 3)

The trajectories were obtained from the following Syntax

trajplot, xtitle(Scaled Age) ytitle(Prevalence)

PROJ TRAJ assigns group membership to each child where the posterior probability in that group is the highest. Parameter estimates are based on maximum likelihood through the quasi-Newton optimization procedures and standard errors are almost by a first order Taylor series expansion (42). Trajectory groups are group of children following almost similar pattern of collection of antibiotics prescription. They do not belong to a trajectory group but are assigned probability of group membership. The cohort follows a continuous distribution; it should not be regarded as concrete or real (45). For example, table 3.2 gives an example of model selection using BIC criterion, and estimated group proportions. The model with 4 groups can be assumed to be best fit model as it has low BIC value, all groups size are above 5%.

			Estimated group proportions				
Group Numbers	**BIC**	**Polynomial Order of each group trajectory**	**Group 1 (%)**	**Group 2 (%)**	**Group 3 (%)**	**Group 4 (%)**	**Group 5 (%)**
1	-18,000	2	100	-	-	-	-
2	-16,788	2, 3	46	54	-	-	-
3	-15,999	2, 1, 3	25	50	25	-	-
4	-15,600	2, 3, 0, 3	10	20	30	40	-
5	-15,100	1, 3, 3, 3, 3	4.7	19.3	9.2	21.5	35.3

Table 3.2 Estimated group proportions should exceed 5.0%. 3 The model with the highest (least negative) BIC value is preferred. Trajectory shapes: 0, constant; 1, linear; 2, quadratic; and 3, cubic. Abbreviation: BIC, Bayesian Information Criterion.

Therefore, in this thesis membership probability is estimated for each child subject to every trajectory. For example, Child A has the membership probability of 72% to trajectory 1, 15%

to trajectory 2, 3% to trajectory 3 and 10% to trajectory 4 in our four group model. The child would be assigned to the trajectory for which child has the highest probability.

The model fitting process of the GBTM is repetitious and demanded running the model several times, changing the number of groups and assigned order each time to generate the best fitting model for the data. When building group-based models we did not have a prior knowledge on deciding number of groups on how prescription of antibiotics changed over time. The following steps were used to generate the best fitting model.

1. Determining the maximum number of groups.
2. Select the optimal order for each group and run models, starting with one group model until maximum number of assigned groups is determined in a stepwise manner.
3. Finalize the model with the appropriate number of groups that best fits the data.

In this thesis the maximum number of groups was limited to 4 for avoiding small size of trajectory groups and for easy understanding of trajectories. It would not be informative to make large number of trajectories with a small number of individuals in each group. Secondly, the shape of trajectory for each group over times was decided based on the correct order of each equation. As per suggestion by Nagin et al., each group should be assigned to a second order at the beginning of the analysis and then keep changing till it reaches an optimal order for the best model (45).

The PROJ TRAJ function can model up to a fourth order polynomial. We started analysis with one group model with quadratic order. Then we ran another models by changing the group from quadratic to linear and cubic till we got significant parameters.

Four groups were preferred in the models. The reason for opting four groups is to find high users of antibiotics, low users and in between both the high users and low users of antibiotics. In our analysis GBTM allows for inclusion of time-varying (seasons, prescriptions) and time stable (sex) predictors simultaneously to enhance the distribution accuracy and adjust the shape of each trajectory group.

The analysis was initially conducted on 10%, 50% and finally 100% of the population. The order were run as (1 1 1), (2 2 2), (3 3 3 3), (1 1 2 2) and other combinations of polynomial functions for the entire population, population in each birth season and population in each gender. Across all distributions, a polynomial function of age determines group membership probability and group shape. The polynomial function is not similar across all individuals. GBTM assumes that trajectory data can be summarized by a finite number of polynomial functions. The possibility exist for each trajectory group to be shown as linear, quadratic or cubic polynomial function. As the polynomial number goes up it adds greater complexity to group shape. The higher order polynomial function would enhance fit if they genuinely provide a better description of data than lower order polynomial.

Goodness-of-fit was evaluated at each step using the Akaike information criterion (AIC) and Bayesian information criterion (BIC; smaller the values, better the model). Models that had values of AIC and BIC nearer to zero or were more negative compared to other polynomial models were selected. The significance of AIC and BIC models is explained in the background section. If a particular model has close to zero percentage of population in one of the group, then that model was abandoned. The group size lower than 5% were accepted in our analysis as the population size is big. Therefore, even below 1% of the group size had more than 1000 children in that group.

3.3 Permissions

The project has all the relevant permissions.

Regional ethical committee: Decision number 2018/1081

“*Med hjemmel i helseforskningsloven §§ 2 og 10 godkjennes prosjektet*

og det gis dispensasjon fra taushetsplikt jf. § 35.

4. Results

4.1 GBTM Trajectories for complete dataset with 184012 children.

A total of 184012 children within age group 0-3 years were included. The table 4.1 shows the distribution of population in our database based on birth season and gender. The study had more males than female population.

Birth season	**Number**	**Percent**
Winter	45084	24.5
Spring	51255	27.8
Summer	48923	26.5
Autumn	38750	21.0
Sex	**Number**	**Percent**
Male	101849	55.3
Female	82163	44.6

Table 4.1 Number of children born as per birth season and sex

Four group trajectory model with order cubic (3 3 3 3) was selected as best model for our study. The conditions for selecting the best fitting model have been explained above. In this 4 group model, four distinct patterns of antibiotic prescription collection were observed during the 0-3 year duration for children. The figure 4.1 shows the output from Stata of our analysis. The table provides us with AIC, BIC values, and group size.

In this 4-group model four distinct pattern of antibiotic prescription collection were apparent during the 36 months follow up. They would be very high level (red color curve), high level (blue color curve), medium level (orange color curve) and low level (green color curve).

```
---- traj Stata plugin ----  Jones BL  Nagin DS,  Build: rev  8 2020

184012 observations read.
184012 observations used in the trajectory model.

                        Maximum Likelihood Estimates
                        Model: Logistic (logit)

                                          Standard        T for H0:
 Group    Parameter         Estimate          Error     Parameter=0    Prob > |T|

 1        Intercept         -4.29152        0.08481         -50.603        0.0000
          Linear             0.42434        0.01505          28.186        0.0000
          Quadratic         -0.00996        0.00087         -11.433        0.0000
          Cubic             -0.00004        0.00002          -2.481        0.0131

 2        Intercept         -6.19004        0.05917        -104.623        0.0000
          Linear             0.31654        0.00969          32.670        0.0000
          Quadratic         -0.00136        0.00051          -2.666        0.0077
          Cubic             -0.00017        0.00001         -20.588        0.0000

 3        Intercept         -5.03060        0.01923        -261.571        0.0000
          Linear             0.50196        0.00410         122.570        0.0000
          Quadratic         -0.02114        0.00029         -72.439        0.0000
          Cubic              0.00019        0.00001          32.534        0.0000

 4        Intercept         -2.18726        0.06728         -32.510        0.0000
          Linear             0.50041        0.01660          30.138        0.0000
          Quadratic         -0.02911        0.00124         -23.490        0.0000
          Cubic              0.00037        0.00003          14.258        0.0000


  Group membership
 1        (%)                1.81779        0.04906          37.056        0.0000
 2        (%)               39.66792        0.72104          55.015        0.0000
 3        (%)               57.78061        0.71837          80.433        0.0000
 4        (%)                0.73368        0.03193          22.980        0.0000

 BIC=-1705679.92 (N=6622648)  BIC=-1705645.88 (N=184012)  AIC=-1705549.71  ll= -1705530.71
```

Figure 4.1 Output from Stata analysis showing BIC and AIC values.

Trajectories in shown in figure 4.2 identified children in following four categories

- The maximum antibiotics prescription collection based on group size of 0.7% of total population. Around 60% of children in this group collected the prescription at 10 months of age (red color curve).
- In the group representing 1.8% of total population. Around 50% of children in this group collected the prescription at 22 months of age (blue color curve).
- In the group representing 39.7% of total population. Around 18% of children in this group collected the prescription at 16 months of age (orange color curve).
- In the group representing 57.8% of total population. Around 17% of children in this group collected the prescription at 24 months of age (green color curve).

The Y-axis represents the proportion of that specific group that got the antibiotic prescription. The X-axis represent the duration in months from the birth till 36 months.

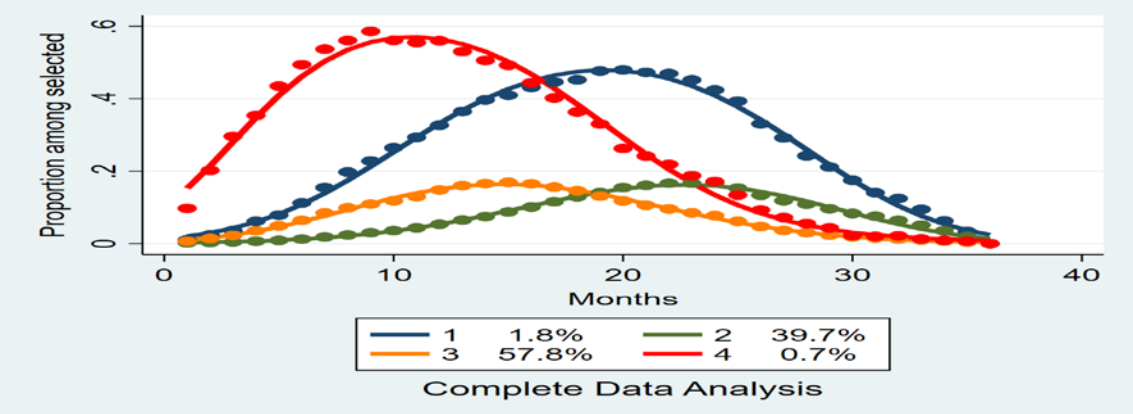

Figure 4.2 Trajectory models using 4 groups. The monthly predicted probability of antibiotic prescription collection in each group is plotted with solid lines. The observed proportion of children in each group that are taking antibiotics is plotted with dots.

	Group 1	**Group 2**	**Group 3**	**Group 4**	**Total**
Group Size	1.81%	39.66%	57.78%	0.73%	100%
Female (%)	1227 (44.1%)	31628 (46.9%)	48895 (43.4%)	413 (35.5%)	82163
Male (%)	1558 (55.9%)	35850 (53.1%)	63691 (56.6%)	750 (64.5%)	101849
Number of Prescription	27789	185267	304566	13974	531596
Average number of prescriptions per children	9.97	2.74	2.70	12.01	2.88
Number of Children	2785	67478	112586	1163	184012
Birth season					
Winter (%)	784 (28.2%)	19087 (28.3%)	24959 (22.2%)	254 (21.8%)	45084
Spring (%)	879 (31.6%)	23419 (34.7%)	26694 (23.7%)	263 (22.6%)	51255
Summer (%)	713 (25.6%)	16437 (24.4%)	31450 (27.9%)	323 (27.8%)	48923
Autumn (%)	409 (14.7%)	8535 (12.6%)	29483 (26.2%)	323 (27.8%)	38750

Table: 4.1 Children Characteristic by Trajectory Using a 4-Group Model

As shown in Table 4.1 the average number of prescriptions in groups with highest and lowest number of children is around 4 folds. Total number of prescriptions given to children in our dataset is 531596 with average being 2.88 per child. Group 2 and group 3 have highest number of children in them and both the groups have average prescription near around 2.7 per child.

The peak for group 2 is highest around 22 months, here the maximum percentage of children are born in spring (34.7%). Therefore, the peaks comes around 22nd month after their birth in spring season, which would be winter season period. Similarly, the peak for group is highest around 15th month, here the maximum percentage of children are born in summer & autumn (27.9% & 26.2%). Therefore, the peaks comes around 17 months after their birth in summer and autumn, which would be winter season.

4.2 Antibiotics prescription collection trajectories as per birth season

The following figure 4.3 compares proportion of antibiotics collected by children born in four birth seasons and their pattern of antibiotic using trajectory models based on (2 2 2 3) order. The model was selected based on its best fit as per criteria mentioned in method section.

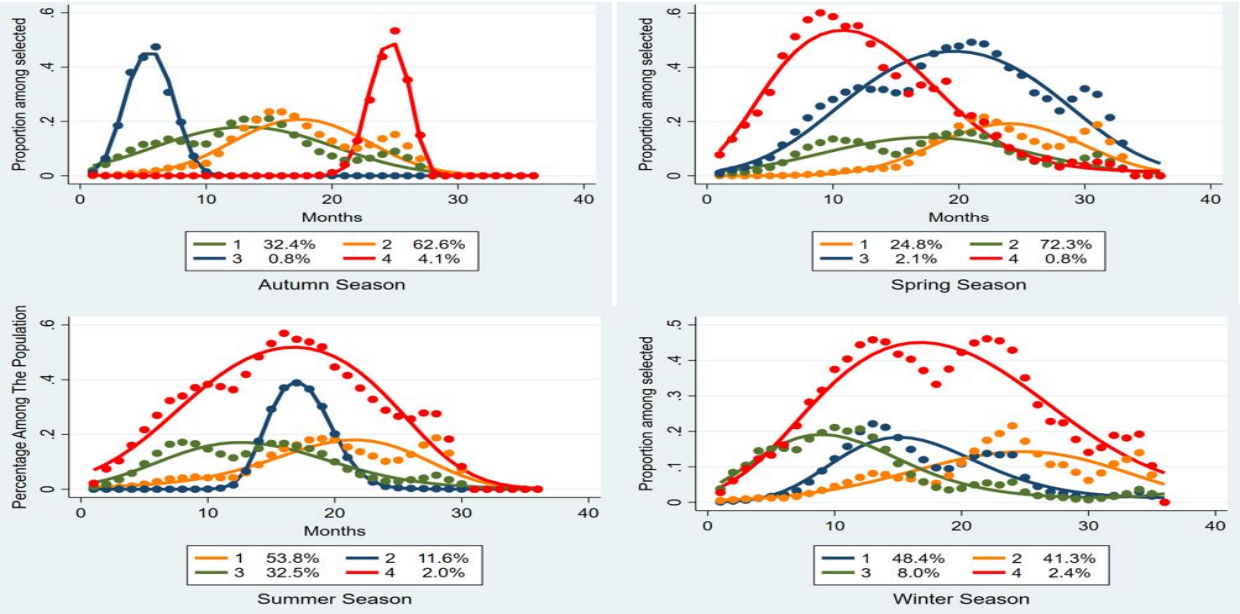

Figure 4.3 Trajectory models using 4 groups. The observed proportion of children in each group as per their birth season (autumn, spring, summer and winter) that collected antibiotics is plotted with dotted lines. Highest proportion (red color curve), high proportion (blue color curve), medium proportion (orange color curve) and low proportion (green color curve).

The highest proportion of children taking prescription have group size from (0.8-4.1%) during the four seasons. Children born in autumn (September-November) would experience winter at (3^{rd}-6^{th}, 15^{th}-18^{th}, 27^{th}-30^{th}) month of age, children born in winter (December-February) would experience winter months at (9^{th}-12^{th}, 21^{st}-24^{th}, 33^{rd}-36^{th}) month of age born in the spring (March-May) would experience winter months at (8^{th} -10^{th}, 20^{th}-22^{nd}, 32^{nd}-34^{th}) of age, those born in summer (June-August) would experience winter at (6^{th}-8^{th}, 18^{th}-20^{th}, 30^{th}-32^{nd}) month of age As per the pseudo birth date Children born on 15 May would be 9 months old on 15 February and children born on 15 April would be 8 months old on 15 December.

- As per trajectories in autumn, group 2 with 62.6% has highest number of children with antibiotics prescription after 15 months. Children in group 4 has highest percentage of prescriptions at 24^{th} month.

- For spring season the group 2 with 72.3% has highest number of children with antibiotics prescription at 10^{th}, 20^{nd} and 32^{nd} month. Even, children in group 4 with maximum percentage of prescriptions the increase is seen during the 10^{th}, 20^{nd} and 32^{nd} month. This corresponds to the winter cycle experienced by children born in spring.

- For summer season the group 1 with 53.8% has highest number of children with antibiotics prescription at 8^{h}, 19^{th} and 29^{th} month. Even, children in group 4 with maximum percentage of prescriptions the increase is seen during the 10^{th}, 20^{nd} and 32^{nd} month. This corresponds to the winter cycle experienced by children born in summer.

- Children born in winter have two major groups with population of 48.4% and 41.3% those in group 1 attain maximum antibiotic usage at 13^{th} and 24^{th} month from the month of birth. Whereas, group 4 in winters the highest percentage of children with prescriptions are in 12^{th} and 24^{th} month. There are two peaks in the group 4 in winters unlike in other seasons.

The following figure 4.4 shows the number of antibiotics prescription collected by age in months (0-35) as per birth season. The star indicates when the children born in that respective birth season experience winter.

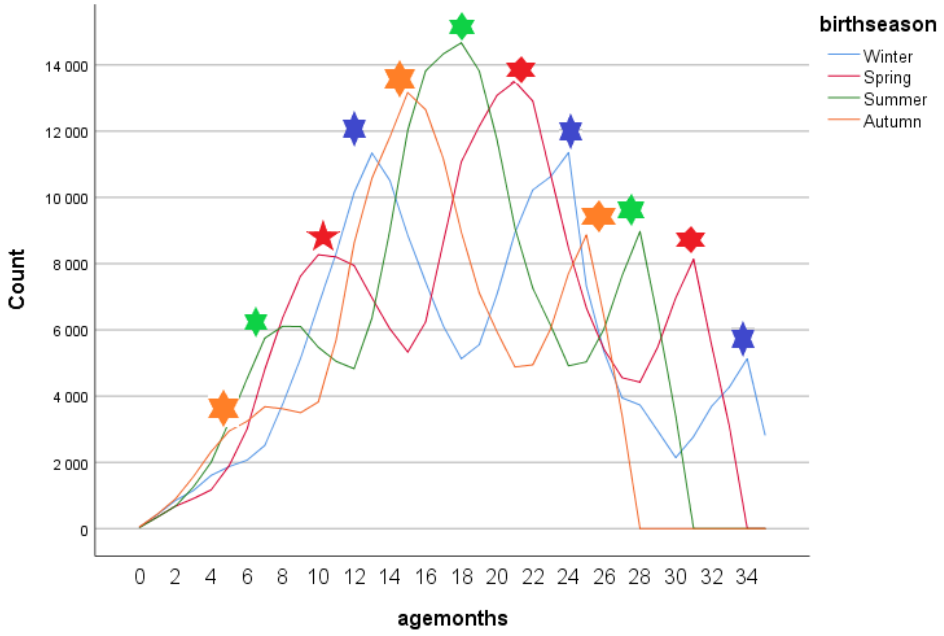

Figure 4.4 Number of antibiotics prescriptions collected based by age in month.

Each birth season has a cyclical order for the collection of antibiotics prescription over three years. Children born in the autumn are among the youngest at risk, as they face winter at age of 2-4 months. This is shown as the small peak at the very beginning of Figure 4.4, the pattern repeats after approximately 12 months. The clear peak for high prescription collection is seen at 11-13 months.

4.3 Antibiotics prescription collection trajectories as per sex

The following figure 4.5 compares proportion of antibiotics prescription collected by girls and boys. The order was run as (2 2 2 3), the model was selected based on its best fit as per criteria mentioned in method section. We observe almost similar trajectories for both the genders. The male population (55%) is higher than female (45%) population in our dataset. The trajectories reflect almost similar size of population in all the four groups.

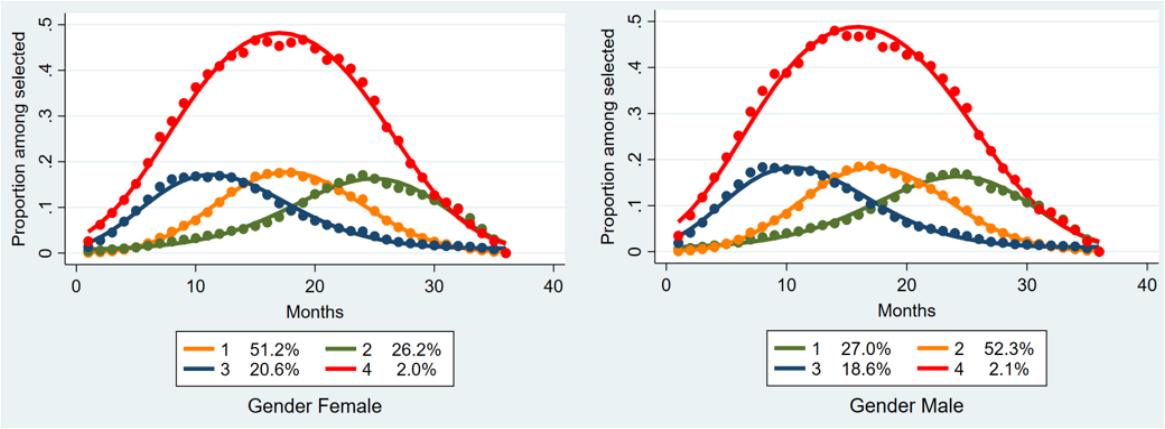

Figure 4.5 Trajectory models using 4 groups. The observed proportion of children in each group as per gender that took antibiotics prescription is plotted with dotted lines.

5. Discussion

In this thesis, we hypothesized that there should exist some association between trajectories obtained from GBTM for total number of prescriptions given in children 0-3 years in Norway. In this study, for children factors (birth season & sex), the probability of being in four groups with different rate of antibiotic prescription collection was obtained. Using GBTM, our second objective of how birth season give different trajectories was achieved. From GBTM, distinct pattern of prescription collection pattern were obtained.

5.1 Antibiotic prescriptions for complete dataset with 184012 children.

The results demonstrate that children have different groups that follow a pattern of collection of antibiotics prescription during the first three years of life. The analysis of dataset reveals that there are distinct groups with significant difference in the average number of prescriptions collected till the age of 3 years. Group 4 with highest proportion of antibiotics prescriptions has 1163 children, though the group size in 0.7%. The proportion of children born in winter in group 4 is lowest among all the groups. As for group 1 has second highest proportion of prescription collection and the average prescription collection is 9.97/child. The group 4 in figure 4.2 has the highest percentage of boys compared to other groups. The higher proportion of children born in winter along with higher proportion of male in same group could be considered as factor for higher prescription collection. A Danish study found that season of birth effected the overall risk of redeemed antibiotic prescriptions (4). There are studies that identified that male gender is at more risk of AOM. A study in Taiwan showed that boys 0-2 years were associated with higher recurrent AOM (61). However, some studies have found that there is no gender difference between incidence and prevalence of AOM (62).

The higher average number of prescriptions in group 4 and group 1 could be due to recurrent respiratory tract infection. As per a study conducted on 1089 children till the age of 2 years, the 10% of children with highest number of annual respiratory illness had a median of 9.6 acute respiratory infections per year (63). Assuming no data error, it could be interesting to explore why there exist peaks with so high proportion of children taking antibiotics, which children in total made up of group 4 in figure 4.2. The group had similar percentage (27.8%) of children born in summer and autumn. As for group 1 the most number of children were born in winter (28.2%) and spring (31.6%). Therefore, the two groups (1 and 4) with highest average number of prescription have no similarity for children born in birth season that should had been same.

A study from Norwegian neonatal medical register recorded early sepsis and exposure to antibiotics agents in the first week of life. The study was conducted from 1 January 2009 to 31 December 2011. It was found that 10,175 (6%) of all preterm infants were hospitalized in the first week of life, among them 39% received intravenous antibiotic treatment (64). The consequence of this antibiotic treatment in hospital means there is group of children who already had high dose of antibiotics in hospital and are probably collecting prescription as a follow up to their treatment. These group of children should be identified as they would have significant impact on average prescriptions as they are regular users of antibiotics due to some illness or treatment. The group 4 with average prescription of 12/child could be having children that were earlier admitted to hospital for treatment.

5.2 Antibiotic prescriptions as per birth season

Our finding show that compared to other seasons, children born in spring have highest group size among those who have collected prescriptions on antibiotics. The group with highest proportion of antibiotic prescriptions had their first peak while they experienced the first winter

season. For children born in autumn the peak in group 3 was after 5-6 months, those born in spring the peak was around 10 months, born in summer the peak was after 8 months and born in winter the peak was after 12 months. This can be linked to study conducted in 5 European countries that showed that increased intake of antibiotics in higher during winter months is due to prescription of antibiotics for treatment of viral infections. (65). It suggests that antibiotics are still used improperly for diseases that are caused by viruses.

5.3 Antibiotic prescriptions as per sex

There are no distinct trajectories pattern among male and female children in our GBTM. A retrospective cohort study in Italy showed that there is modest gender difference for children under the age 24 months for usage of respiratory tract drugs (5). There has been a study that showed lower frequency of antibiotics treatment in girls than boys could be attributed to social factors. The study was conducted in South Asian countries (8). The same could not be said about Norway as there is more even distribution of socioeconomic structure. This could be one of the factor we observe similar trajectories for boys and girls.

The GBTM is based on the idea that individual following the same developmental course may have peculiar characteristics which differ from other groups and they may follow different developmental courses during time.

5.4 Strength of study

The strength of our study is the complete data set with a personal identifier. The use of GBTM helped to show the patterns in different trajectories and what characteristic mattered in distinguishing differences among children in different groups in regards proportion of

antibiotics prescription collection. The data into trajectory groups, GBTM methodology to study the antibiotic prescription pattern in children provides a strong statistical tool to summarize large data in an easily understandable model. It is assumed that GBTM allows to discover hidden groups within the population that follow a different development trajectories. We opted months instead of 1 week as it would had generated ample signs on the group making it harder to interpret, 3 months interval would had made us loose the information.

The other strength of GBTM for analyzing prescription pattern over time is that it is easily understandable graphically and it provides easy and provides tabular data summaries. This method takes into account the covariates, missing outcome and patterns within the same model (66). GBTM has advantages over other models used to study longitudinal data. It assumes that subgroups are part of the population but each group follows independent development pathways (47). GBTM are significant for groups that display more variation in prescription collection over time.

5.5 Limitations

NorPD captures the prescriptions to children in Norway but has less information about chronic disease in children. There can be differences in prescription pattern based on prescriber practice, geographical healthcare units, and expectations of parents of children (67). In the method, we describe how pseudo age is defined as date of prescription minus pseudo age of birth here we have margin of error of a maximum of 16 days.

GBTM can group individuals with similar course pattern. This modelling technique does not considers within-group variability, the variability of individual trajectory in the same course pattern. This would give different results compared to growth mixture modelling

and growth curve modelling (56). GBTM depends substantially on the professional perception of the investigator. This is particularly regarding the number of trajectories and the type of change (linear, cubic etc.) to be defined. Therefore, it is important to evaluate the existing literature on the variable (antibiotic prescription for this study) to understand the pattern they currently follow. Further, there was no information regarding the quantity of antibiotics prescribed in the prescription. The packet size of antibiotics could be with 10, 20, 30 or more doses. Therefore, children that receive high number of doses to be taken for longer duration would have less prescriptions compared to those who receive less doses for similar illness, they would be required to collect new prescription for more doses. To explain more about the antibiotic prescription collection several prescriber and patient variable could be included.

We should also have information if the child had received any treatment in the hospital during newborn period. It could be that these children are high collectors of antibiotic prescription. It might be useful to be able to map children with high or low risk of asthma or other chronic diseases that might affect use of antibiotics before prescribing antibiotics. The prescription registry data could have more information on confounding factors that might be relevant to antibiotic prescription. The confounding factors could be method of delivery (normal or caesarean), siblings, passive smoking, socio economic factors, pre-pregnancy BMI. The anatomical therapeutic classification (ATC) codes could had been also taken into account as confounding factors. It may be argued that our description of antibiotic use applies to a setting that is somewhat unusual.

NorPD captures all dispensation of antibiotics from pharmacies to individuals. Data is considered valid and electronic records of prescription is required by law (57). Register data is

not affected by information and recall bias due to self-reporting of the drug use. However, as per the Norwegian medicine act 17 doctors can be given permission by Ministry to deliver medicines and other nursing items for fees if access to a pharmacy is cumbersome. It happens only with patients being far from pharmacies (60).

It constitutes a small proportion and would not affect our estimates. Children have high prevalence of antibiotic users, and it is important to map the effect or lack of effect of measures related to prescribing in this age group. The proportion of registration with pseudo national ID number was highest during the early study period of 2004 to 2007. The problem with NorPD data is that we cannot be really sure if the collection of antibiotics from pharmacy actually consumed by children at home. We cannot validate if the dispensed antibiotics are used appropriately or inappropriately.

6. Conclusion

In this thesis we used GBTM to address the prescription patterns of antibiotics among children. It does so by defining trajectory groups based on number of prescriptions and time from birth to collection of prescriptions. This method as per best of my knowledge has not been used for antibiotics prescription in children 0-3 year age in other studies. Also, further studies to qualify the way to use other variables and clarify the accuracy of the dataset and needed to determine how the children should be accurately grouped to test which factors are associated with specific groups. Our results do not suggest marked differences among children born in birth seasons and the association of to the trajectories showing proportion of antibiotics prescription collected.

Future, research on trajectory modeling should focus on inclusion of other factors that might possibly be affecting the outcome. There could be differences in prescription pattern for children based on the geographical location in Norway. For example, a Norwegian study found that residents in municipality with high consultation rates received 42% more prescription for RTIs compared to area with low consultation rates. The study included all municipalities with more than 5000 residents in 2014 (68). This factor could be considered for future studies in children.

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