

Clinical indications for antibiotic use in Danish general practice: results from a nationwide electronic prescription database

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ABSTRACT

Objective: To assess the availability and applicability of clinical indications from electronic prescriptions on antibiotic use in Danish general practice.

Design: Retrospective cohort register-based study including the Danish National Prescription Register.

Setting: Population-based study of routine electronic antibiotic prescriptions from Danish general practice.

Subjects: All 975,626 patients who redeemed an antibiotic prescription at outpatient pharmacies during the 1-year study period (July 2012 to June 2013).

Main outcome measures: Number of prescriptions per clinical indication. Number of antibiotic prescriptions per 1000 inhabitants by age and gender. Logistic regression analysis estimated the association between patient and provider factors and missing clinical indications on antibiotic prescriptions.

Results: A total of 2,381,083 systemic antibiotic prescriptions were issued by Danish general practitioners in the study period. We identified three main clinical entities: urinary tract infections ($n = 506,634$), respiratory tract infections ($n = 456,354$) and unspecified infections ($n = 416,354$). Women were more exposed to antibiotics than men. Antibiotic use was high in children under 5 years and even higher in elderly people. In 32% of the issued prescriptions, the clinical indication was missing. This was mainly associated with antibiotic types. We found that a prescription for a urinary tract agent without a specific clinical indication was uncommon.

Conclusion: Clinical indications from electronic prescriptions are accessible and available to provide an overview of drug use, *in casu* antibiotic prescriptions, in Danish general practice. These clinical indications may be further explored in detail to assess rational drug use and congruence with guidelines, but validation and optimisation of the system is preferable.

ARTICLE HISTORY

Received 9 November 2016

Accepted 27 April 2017

KEYWORDS

Antibiotic prescribing; clinical indication; general practice; electronic prescriptions; data linkage

Introduction

The development of antimicrobial resistance is a major challenge to modern medicine [1]. Antimicrobial prescribing is directly linked to the development of antimicrobial resistance [2,3], therefore it is necessary to minimise overuse and misuse of antibiotics in everyday practice. National and international efforts to reduce antibiotic use have been promoted [4,5], but despite these initiatives, the use of antibiotics in the primary care sector remains high and broad spectrum use is increasing [6]. We do not know whether the observed antibiotic use pattern is clinically justifiable and due, in part, to an ageing population with a high degree of multimorbidity.

Extrapolations from general measures of antibiotic use by county and country [6,7] do not permit an assessment of the clinical relevance or appropriateness of individual prescriptions, nor do they support the assessment of antibiotic use patterns in specific infections according to guideline recommendations. One shortcoming in understanding issues of appropriate antibiotic use is the lack of data on clinical indications. It is difficult to evaluate the appropriateness of an antibiotic prescription without knowledge of clinical presentation, i.e. the patient's medical history and the physical examination of the patient by a health professional.

The United Kingdom has successfully addressed this problem by applying data linkage from Read Codes,

the alphanumeric codes that refer to clinical terms in a general practice database, to data on antibiotic use. This effectively surveys use of antibiotic types as well as the efforts to implement measures to control or change antibiotic prescribing [8,9].

Although data linkage in Danish general practice is theoretically feasible, it is not possible by law to assess prescribing and antibiotic use directly through a specific general practice database. However, a nationwide system of electronic prescriptions was created in 2009, and fully implemented in 2011. As a consequence, doctors must enter a clinical indication from a pre-specified, drop-down menu, or by entering free text, to justify their prescription. Introducing standardised clinical indications on electronic prescriptions has also embedded the promotion of rational prescribing and might be used in attempts to run pharmaco-epidemiological surveys in Denmark.

In this study, we aim to assess the availability and applicability of clinical indications from electronic prescriptions on antibiotic use from July 2012 to June 2013 in Danish general practice.

Materials and methods

Data sources

Our study included all Danish citizens who redeemed an electronic antibiotic prescription during the period 1 July 2012 to 31 June 2013.

We extracted national data on the use of antibiotic therapy in Denmark from the Danish National Prescription Register [10]. Since 1 January 1995, this registry contains information on all prescriptions redeemed by Danish residents at outpatient pharmacies. Registered drugs are categorised according to the WHO's Anatomical Therapeutic Chemical Classification System (ATC). We used the case category J01: antibacterial agent for systemic use. Information was available to ATC level 5 (chemical substance) [11]. In Denmark, antibiotics are only available by prescription and primary non-compliance is low (3%) [12], making the register virtually complete.

For each redeemed prescription, the registry contains information on the following variables relevant to this study: patient social security number (encrypted), provider practice identification number (encrypted), type of antibiotic (ATC 5th level), age, gender and clinical indication. A clinical indication must be entered when prescribing an antibiotic in the electronic prescription system. The available preset indications differ between antibiotic types, e.g. penicillin V (J01CE02) has more than 15 possible specific

indications (e.g. acute otitis media, pneumonia, etc.), while mecillinam (J01CA11) has two specific indications (urinary tract infection and cystitis). An unspecific indication "Infection" is available for all antibiotic types and lastly the general practitioner (GP) may choose to enter a free text indication. Presently the clinical indications are not formally validated such as ICPC-2 codes [13].

Information on practices and the associated providers was accessed through the Danish Health Service Provider Register. Practice and provider details are updated four times yearly and include type of practice (solo or group), doctors' age, gender and affiliation to practice (owner or non-owner) and if doctors in training are present. Practice details include postal code for geographical location and number of listed patients.

We extracted population statistics from www.statistikbanken.dk.

Data sets and variables

General practices were identified by their unique identifying code (encrypted) to distinguish GP prescriptions from those issued by other providers in the primary care sector. We calculated provider age as the mean age of all providers in practices and we reported gender as male/female or mixed if different genders were working together in a practice. To investigate a possible effect of loss of information by calculating a mean age and including the category mixed gender, we also performed analyses only on solo practices.

Selected clinical indications from the electronic prescription system were grouped according to anatomical site, disease characteristics and type of treatment (cure or prevention). These clinical entities were (1) upper respiratory tract infection (URTI) (acute otitis media, acute tonsillitis, acute rhinosinusitis); (2) lower respiratory tract infection (LRTI) (pneumonia, acute exacerbations of chronic obstructive pulmonary disease, acute bronchitis); (3) urinary tract infection (UTI) cure; (4) UTI prevention; (5) skin (impetigo, cellulitis, wound infection, infected eczema, staphylococcal infection); (6) acne; (7) gastrointestinal infection (diarrhoea, gastroenteritis, gut infection); (8) genital infection (chlamydia, epididymitis, pelvic infection); (9) other infections (borreliosis, bite wounds, stomach ulcers, antibiotic prophylaxis, pertussis, malaria, etc.); (10) unspecified infection; and (11) missing indication.

We categorised patient age into six groupings: <5 years; 5–14 years; 15–44 years; 45–64 years; 65–74 years; and 75+ years.

All inhabitants of Denmark are eligible to register with a GP, and GPs are responsible for serving patients

Table 1. Clinical indications for antibiotic prescribing in Danish general practice.

Clinical indication	Antibiotic prescriptions		Age group					
	N	%	<5	5 to <15	15 to <45	45 to <65	65 to <75	>=75
Upper respiratory tract infection	265.277	11	58.654	37.689	104.220	46.937	11.927	5.850
Lower respiratory tract infection	191.256	8	17.660	5.805	36.846	55.695	35.445	39.805
Skin	135.617	6	3.760	9.137	47.111	38.733	17.585	19.291
Acne	37.620	2	50	2.771	29.198	4.322	853	426
Urinary tract infection (cure)	454.650	19	4.691	9.490	123.508	98.983	78.309	139.669
Urinary tract infection (prevention)	51.984	2	112	193	1.864	7.484	9.101	33.230
Gastroenteritis	14.533	1	66	227	5.527	4.996	2.299	1.418
Genital infections	18.484	1	95	170	15.190	2.165	528	336
Other	26.310	1	962	1.348	9.335	6.599	3.605	4.461
Unspecified infection	416.354	17	28.376	22.514	132.872	121.360	59.791	51.441
Subtotal indication	1.612.085	68	114.350	89.291	505.934	388.734	219.753	294.023
Missing indication	768.998	32	52.239	40.020	234.756	198.090	110.219	133.674
Total	2.381.083	100	166.589	129.311	740.690	586.824	329.972	427.697

Upper respiratory tract infection: acute otitis media, acute tonsillitis, acute rhinosinusitis.

Lower respiratory tract infection: pneumonia, acute exacerbations of chronic obstructive pulmonary disease, acute bronchitis.

Other: borreliosis, bite wounds, stomach ulcers, antibiotic prophylaxis, pertussis, malaria etc.

on their list [14]. In general, Danish GPs are required to be open for enrolment of up to a minimum of 1600 patients. Newly opened practices and practices that are closing may have fewer patients. Practices with a list size of fewer than 500 patients were excluded from our study as we felt they were non-representative of Danish general practice. If only one GP was registered to a practice, we classified it as a solo practice. The remaining practices were categorised as group practices. Training practices were identified by specific codes pertaining to junior doctors in residency. We constructed variables concerning “busy” practices as the number of listed patients, and as the number of consultations per listed patient. We looked at practice location according to whether or not it served the richest one fifth of the 98 Danish municipalities (measured as percentage of inhabitants with an income in the top 1%), and also by geographical region [15].

Data from the two national registries were merged to create a data set for analysing the availability of clinical indications from electronic antibiotic prescriptions. To ensure the data set contained data exclusively from general practice, we merged the data sets using the unique practice identification codes. The 1-year study period from July 2012 to June 2013 included an entire winter season [6] in order to capture any outbreaks of infection that last from one calendar year into the next.

Analyses and statistics

We applied descriptive statistics to characterise antibiotic use. We calculated the number of prescriptions per 1000 inhabitants at each year of age in the range from birth to 100 years and present number of

redeemed prescriptions by clinical indication for the six age groups.

To assess differences between electronic prescriptions with and without clinical indications we investigated factors associated with missing indications. Logistic regression models were constructed with the dichotomised variable missing indication (yes/no) as the outcome, and antibiotic type, patient and provider characteristics as explanatory variables. We made adjustments for excess correlation between prescriptions/patients within practices by generalised estimating equations methods. Both univariable and multivariable analyses are presented.

All calculations were made in SAS version 9.4 (Cary, NC, USA).

Results

A total of 2.381.083 systemic antibiotic prescriptions (ATC J01) were redeemed in Denmark in the 1-year study period by 975.626 individual patients. A clinical indication was assigned by the GP in 1.612.085 (68%) of the prescriptions. In 768.998 (32%) of the prescriptions, the clinical indication was missing. The antibiotic use rate per 1000 inhabitants per year by age group was 532 in children younger than 5-year olds; 195 in 5–15 years; 348 in 15–45 years; 392 in 45–65 years; 555 in 65–75 years; and 1054 in patients aged more than 75 years.

Indications for antibiotic prescriptions

For the 1.6 million prescriptions in which a clinical indication was assigned, three roughly equal sized infection groups constituted the majority of prescriptions; (i) UTI (cure and prevention), $n=506.634$, (ii) acute respiratory tract infection (URTI and LRTI),

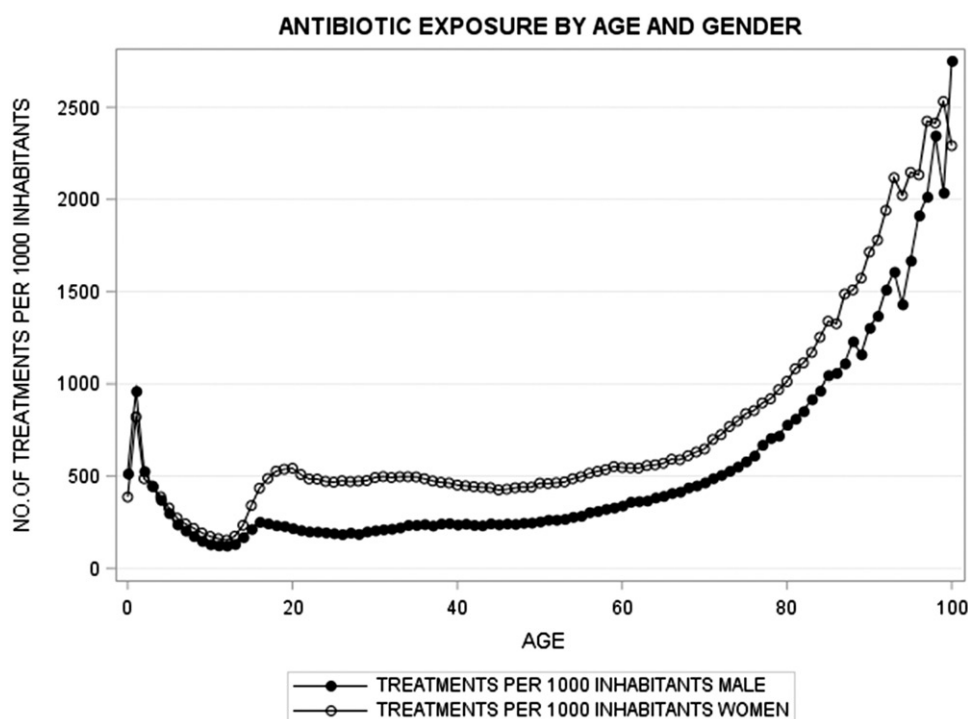


Figure 1. Antibiotic exposure by age and gender. Danish general practice 2012–13. Antibiotic use is high in children less than five years of age of both sexes. Women experienced a steep increase in antibiotic use from their late teens and their use stayed elevated until the age of 90, compared to men. In people aged 20–60 years the antibiotic use is at a stable level for both sexes.

$n = 456.356$ and (iii) non-specific indication “Infection”, $n = 416.354$ (Table 1). Among LRTIs ($n = 191.256$), pneumonia was the most common clinical indication accounting for 93% (178.354/191.256) of the prescriptions. Skin infections were also frequent, making up 8% ($n = 173.237$) of the redeemed antibiotic use. The number of prescriptions by patient age group and clinical indications varied as presented in Table 1. The number of unspecific and missing indications was evenly distributed between patient age groups.

Elderly people aged ≥ 65 years were prescribed more antibiotics than younger patients (Figure 1). This finding was particularly striking in male patients diagnosed with UTIs as almost half of these prescriptions (43.000/92.000) were issued for patients aged ≥ 75 years (Table 1). Children younger than 5 years were also prescribed antibiotics at a higher rate than older children and people in middle age.

We found a steep increase in antibiotic prescribing for women in their late teens (Figure 1). Overall, women received almost twice as many prescriptions as men (female:male ratio 1:8). If UTI-related prescriptions were omitted, this ratio dropped to 1:3.

Prescriptions with missing indications

We observed a high degree of variation in the number of electronic prescriptions with missing indications

between practices, ranging from fewer than 10% to more than 90%.

Prescribing a urinary tract agent (trimethoprim, nitrofurantoin, mecillinam or sulphamide) halved the incidence of a missing indication on an electronic prescription (OR 0.50, 95% CI 0.48–0.52). An increase in the incidence of a missing indication was associated with a prescription of a macrolide antibiotic (OR 1.16, 95% CI 1.12–1.20) or scripts issued by a GP in a solo practice (OR 1.27, 95% CI 1.07–1.51). Large list sizes or “busy” practices did not seem to affect the proportion of missing indications. We found no association between GP age and incidence of missing indications (OR 0.98, 95% CI 0.76–1.27) in the primary analysis. Restricting the analysis to solo practices did not change this estimate (OR 1.04, 95% CI 0.97–1.12) (Table 2).

Being a GP in a rich municipality did not significantly alter the incidence of prescriptions with missing indications (OR 0.88, 95% CI 0.75–1.03). However, we did observe an uneven geographical distribution, as the Capital Region and Western Jutland had higher proportions of missing indications (data not shown). The GP female:male ratio for prescriptions with missing indications was 1:6.

Prescriptions with non-specific indications

Prescriptions with non-specific indications were not associated with the issued antibiotic being a UTI agent

Table 2. Factors associated with missing indication on antibiotic prescriptions from Danish general practice 2012–13.

Variable	Univariable odds ratio (95%CI)	Multivariable odds ratio (95%CI)
Antibiotic type		
Penicillin V	1.0 Reference	1.0 Reference
Macrolide	1.18 (1.14–1.22)	1.16 (1.12–1.20)
Quinolone	1.13 (1.07–1.20)	1.05 (1.00–1.11)
Urinary tract agent ^a	0.54 (0.52–0.57)	0.50 (0.48–0.52)
Other antibacterials	0.95 (0.92–0.98)	0.93 (0.90–0.96)
Patient characteristics		
Patient age (10 year increase)	1.01 (1.00–1.01)	1.04 (1.03–1.04)
Male	1.12 (1.10–1.13)	0.99 (0.98–1.00)
Practice characteristics		
Solo practice	1.09 (0.99–1.21)	1.27 (1.07–1.51)
GP gender		
male	1.0 Reference	1.0 Reference
female	1.01 (0.89–1.14)	1.11 (0.96–1.27)
mixed (group practice)	1.04 (0.92–1.17)	1.30 (1.09–1.56)
GP age (10 year increase) ^b	1.01 (0.97–1.05)	0.98 (0.93–1.04)
List size (increase by 1000 patients)	1.13 (0.97–1.31)	1.13 (0.97–1.31)
"Busy" practice ^c	0.99 (0.93–1.06)	0.99 (0.91–1.07)
Tutor practice ^d	0.98 (0.76–1.27)	0.98 (0.76–1.27)
Practice location (rich municipality) ^e	0.89 (0.74–1.04)	0.88 (0.75–1.03)

Regression models adjusted for excess correlation between prescriptions/patients within practices by generalised estimating equation methods.

^aUrinary tract agent: trimethoprim, nitrofurantoin, mecillinam or sulphamide.

^bRestricting the analysis to solo practice (OR 1.04 (95%CI 0.97–1.12)).

^cEstimated as number of consultations per listed patient.

^dPractice receiving doctors in training.

^eUpper quintile of municipalities of citizens with top 1% incomes.

(OR 0.05, 95%CI 0.02–0.09) or quinolone (OR 0.52, 95%CI 0.44–0.5). Otherwise the results between prescriptions with non-specific indications and those with missing indications were comparable regarding patient and provider characteristics. The patient female:male ratio was 1:3, which was comparable to the ratio present in prescriptions without UTI agents (1:3).

Discussion

Principal findings

We have used clinical indications from electronic prescriptions to provide an overview of antibiotic use in Danish general practice. We suggest that our method could provide information on rational antibiotic prescribing by linking individual prescriptions to the corresponding clinical indications. However, the issue of high numbers of missing and unspecified indications must be addressed prior to the widespread use of this approach.

We identified three main clinical entities in our study with roughly the same number of prescriptions; namely UTIs ($n=506.634$), respiratory tract infections ($n=456.354$) and unspecified infections ($n=416.354$). In 32% of the prescriptions issued, the clinical indication was missing. This lapse was mainly associated with antibiotic types. For example, we found that a prescription for a urinary tract agent without a specific clinical indication was uncommon.

About one fifth of the Danish population was exposed to an antibiotic in 2012–2013 and the majority was issued to females. The antibiotic prescribing rate was high in children under 5 years, and even higher among elderly people (especially the very old).

Strengths and weaknesses of the study

The study is based on nationwide routine data suggesting that the findings are as close to everyday practice as possible and that they may be generalised to similar healthcare systems. In addition, data were collected electronically and independently of the study, minimising information bias.

The large sample improves statistical precision. However, when assessing antibiotic use caution must be exercised as one in three prescriptions had a missing clinical indication. Some of these could be due in part to handwritten scripts and telephone prescriptions, but the major factor was most probably related to the option of entering indications in free text in the electronic prescribing system.

When GPs prescribed a UTI agent, the incidence of a missing indication was halved. This may be explained in part by the drop-down list of clinical indications from which the GP must choose. The available options regarding UTI agents may be more readily available (i.e. at the top of the list, no need to scroll to select the appropriate clinical indication). Also, clinical

uncertainty may be lower in patients with suspected UTI, where clinical signs may be more suggestive of the site of infection and several point-of-care tests are available and used extensively in Danish general practice [16]. This is in line with the low number of UTI agents observed in the non-specific clinical indication "Infection". Also, the fact that GPs when prescribing an UTI agent in the electronic prescribing system had few clinical indications to choose from, compared to penicillin V and macrolides, was likely an important factor.

The season we analysed (July 2012 to June 2013) may be regarded as a standard year in relation to infectious epidemiology as there were no epidemics or infectious outbreaks during the year, except for the recurring influenza season [17]. We were unable to distinguish between day-time and out-of-hours prescribing. However, this may be of minor importance to the overall findings as the contribution from out-of-hours to the entire antibiotic use in Danish general practice was less than 6% in 2014 (unpublished data from Zealand Region).

Findings in relation to other studies

In contrast to previous studies [18–20], we found that the number of antibiotic prescriptions for UTIs was similar to the number issued for respiratory tract infections. This finding may be explained by the fact that a major proportion of the scripts assigned an "unspecific indication" might be related to patients diagnosed with an acute respiratory tract infection. Virtually no UTI agents were labelled with an unspecific indication. However, it could also in part be due to an expectant approach to acute respiratory tract infections including non-antibiotic management strategies and that few Danish GPs report a high level of perceived patient pressure for antibiotics [21].

Shapiro et al. [22] found a prescribing rate of 562 per 1000 children less than 5 years of age which is comparable to our findings. Alarming, our study suggests that antibiotic use among the elderly is higher than in the USA.

Elderly patients over 80 years of age exhibited high antibiotic exposure rates as previously shown [6,23]. This corresponds to three out of four patients in this age category being prescribed an antibiotic in 2012–2013. However, this finding might be due to a subgroup of patients who are high users of antibiotics. Elderly patients more often present with multiple, concurrent chronic conditions and doctors may prescribe antibiotics to play safe. Still, this is worrisome and further studies should look into this particular problem.

Gender differences in antibiotic exposure were evident (Figure 1), and this study confirms previous findings that women are more frequently prescribed antibiotics. The largest difference is observed between the ages of 15–45 years and may primarily be ascribed to an increase in UTI cases among women in this age group [24]. This finding highlights the need to promote tools to ensure a rational prescribing pattern for UTIs [25].

Meaning of the study

We have demonstrated the availability and potential applicability of using clinical indications to characterise drug use, *in casu* antibacterial therapy, from the Danish National Prescription Registry.

Notably, in Denmark in 2014 the introduction of Fælles Medicin Kort [Shared Medication Record] to the electronic prescription system, made participation mandatory by law. Also, the selection of a non-specific indication such as "Infection" was removed from the drop-down list in the system. However, the number of missing indications is constant at roughly one in three prescriptions (Email correspondence with Sundhedsdatastyrelsen–October 2016). This could be due to the fact that free text indications are coded as missing indications, and that the list of possible indication options is not exhaustive. It is also noteworthy that this system may in fact actively (but unintentionally) support diagnostic drift, e.g. the post-hoc justification of a specific drug [26]. This is due to the limited number of available clinical indications only belong to conditions for which antibiotics are recommended. For example, "grey zone" antibiotic use for common cold or diarrhoea is not reflected in the present system. A review of the drop-down codes, and the exclusion of unspecific codes, could be used to improve understanding of antibiotic use for the selected clinical indications. Also, the validity of the clinical indications should be assessed. Alternatively, a direct link to medical records could enable the information from ICPC-2 codes.

It is unknown if the clinical indications assigned on the prescriptions are similar to the International Classification of Primary Care codes assigned in the medical records for the same consultation. Furthermore, it is not clear to what extent the introduction of this feature, to assign a clinical indication prior to signing off an antibiotic, has made an impact on rational antibiotic use patterns. Studies that address these questions are highly needed.

Of note, the present study concerns patients who actually redeemed an antibiotic, i.e. antibiotic use, and will not assist in the assessment of a rational prescribing pattern, examples were diagnostic criteria for the

indication met. However, the data could be used to assess compliance with first-line antibiotic therapy according to guideline recommendations in different clinical entities such as respiratory, skin or urinary tract infections.

Ethical approval

The study was approved by the Danish Data Protection Agency (J.nr. 2012-41-0159). According to Danish law no approval from an ethics committee is required for strictly registry-based studies.

Acknowledgements

We wish to thank Dagny Ros Nicolaisdottir for excellent help with data management.

Disclosure statement

All authors declare no competing interest or potential conflicts of interest.

Funding

RA is funded by a grant from Danish Council on Antibiotic use and Helsefonden (13-B-0196).

Notes on contributors

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Malene Plejdrup Hansen is a medical doctor and a senior research fellow. Malene's research interests include optimising GP's management of patients with acute respiratory tract infections and the evidence for benefits and harms of using antibiotics.

Volkert Siersma is a mathematician and statistician. Volkert has extensive experience in quantitative research projects relevant to a primary care setting. Volkert has a particular interest in epidemiological modeling of individual data collected at various time points.

Lars Bjerrum is a professor at the University of Copenhagen. He is also a general practitioner and specialist in clinical pharmacy. Lars' research interests include diagnostics and treatment of infectious diseases as well as the development of clinical indicators for prudent antibiotic use in general practice.

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