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Increasing prevalence of chronic hepatitis B virus infection and low linkage to care in Denmark on 31 December 2016 - an update based on nationwide registers.

Increasing prevalence of chronic hepatitis B virus infection and low linkage to care in Denmark on December 31, 2016 – an update based on nationwide registers

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Abstract

Objectives: We aimed to update the estimated prevalence of both diagnosed and undiagnosed chronic hepatitis B virus infection in Denmark. Moreover, we aimed to determine the number of people with chronic hepatitis B virus infection in specialized care, and to assess the completeness of reporting to the national register of communicable diseases.

Methods: Using four registers with national coverage, we identified all individuals registered with chronic hepatitis B virus infection, aged 16 years or older, and alive in Denmark on December 31, 2016. The diagnosed population was then estimated using capture-recapture analysis. The undiagnosed population was estimated using data from the Danish pregnancy screening program.

Results: We estimated that 14,548 individuals were living with chronic hepatitis B virus infection corresponding to 0.3% of the Danish population. Of them 13,530 (93%) were diagnosed and 7,942 (55%) were registered in one or more of the source registers. Only 4,297 (32%) diagnosed individuals had attended specialized care and only 3,289 cases (24%) were reported to the Danish communicable disease register.

Conclusion: The prevalence of chronic hepatitis B virus infection increased from 2007 to 2017. The majority that had been diagnosed did not receive care as recommended by national guidelines and were not reported to the communicable diseases register responsible for hepatitis B virus surveillance. Future efforts should focus on linking individuals diagnosed with chronic hepatitis B virus infection to specialized care and improving reporting to the hepatitis B virus surveillance system.

Keywords: Prevalence; Chronic Hepatitis B Virus infection; Denmark; Capture-recapture.

Introduction

Chronic Hepatitis B Virus (HBV) infection affects 296 million people worldwide and was related to an estimated 820,000 deaths in 2015 [1]. Consequently, the World Health Organization (WHO) has set a goal of eliminating viral hepatitis as a public health threat by 2030. To achieve elimination the WHO target is that 90% with chronic HBV infection should be diagnosed and at least 80% of all eligible should receive treatment [2].

Hepatitis B vaccination is not part of the Danish childhood vaccination program, as this is not considered cost effective, due to low incidence. Moreover, acute infections are mainly reported in adults belonging to groups with increased risk including persons with intravenous drug use, men who have sex with men (MSM), persons from high endemic areas and their children [3] Instead, universal screening for HBV infection in pregnancy, and vaccination of children born to HBV infected mothers, have been recommended since 2005. Moreover, national guidelines recommend screening and vaccination of persons at increased risk of infection [4]. It is recommended that all persons with chronic HBV infection are referred to specialized care for management and antiviral treatment if indicated. HBV infection is a notifiable disease in Denmark, based on written reporting by the diagnosing doctor. It is well known that reporting from clinical doctors is incomplete, but until now no laboratory based reporting has been implemented [5]. Therefore, we previously used capture-recapture methods to estimate the size of the population diagnosed with chronic HBV infection in Denmark based on four registers with national coverage [6]. Moreover, we used the pregnancy HBV screening program to estimate the number of people with undiagnosed chronic HBV infection. Overall, we found an estimated prevalence of 10,668 (0.24%) by the end 2007. The cascade of care is used for several infectious diseases to describe the treatment continuum from infection to successful treatment [7]. We wanted to use a cascade of care model to identify areas where increased efforts could have the greatest effect on key goals. Therefore, to guide future elimination strategies the objective of this study was to provide updated estimates on three key elements of the cascade of care for chronic HBV infection in Denmark. The prevalence of chronic HBV infection, the number diagnosed with

chronic HBV infection and the amount of people linked to care for chronic HBV infection. Moreover, we aimed to assess the completeness of reporting to the communicable diseases register, responsible for HBV surveillance in Denmark.

Methods and materials

Data sources

Personal identification numbers unique for each resident in Denmark are used in all national administrative registers, which makes crosslinking of data in large national registers highly reliable.

For the present study the civil register provided information on age, sex, residence, vital status, country of origin and emigration/immigration [8], and the medical birth register provided information on women with chronic HBV infection who gave birth in 2005-2016 [9].

We identified persons with chronic HBV infection in four nationwide registers. All have been described in detail previously [5,10–12]. The case definition varied by register due to different data content. The registers and their case definition are detailed below.

Clinical hepatitis database (DANHEP)

DANHEP was initiated in 2002 and holds demographic, clinical and laboratory data on all patients, at least 16 years of age, who are receiving care for chronic hepatitis B or C in a specialized hospital department. Data from the latest visit are recorded annually for all with chronic hepatitis B or C [10]. Chronic HBV infection in DANHEP was defined as registration and at least one positive HBsAg. Moreover, individuals registered in DANHEP were considered linked to care.

Laboratory database (DANVIR)

DANVIR has since year 2000 collected results of tests for hepatitis B and C from laboratories [11]. As in the previous study, chronic HBV infection in DANVIR was defined as two positive HBsAg tests at least 6 months

apart, or only one positive HBsAg measurement and a negative HBc-IgM at the same time or only one positive HBsAg measurement, no HBc-IgM reported and an HBV endemic country of origin [6].

The National Patient Register

The national patient register was established in 1977 and records dates, diagnoses, and treatments from all in-, and since 1995, out-patients visits in Danish hospitals. Diagnoses are provided by the treating physician [12]. Chronic HBV infection in the national patient register was defined as ICD10 codes B18.0 and B18.1.

The communicable diseases register

Reporting newly diagnosed acute hepatitis B to the communicable disease register has been mandatory since 1980. Notification of chronic HBV infection became mandatory in the year 2000. Notifications are made by the diagnosing physician. Diagnoses are re-evaluated upon notification based on lab results and clinical information [5]. The case definition in this register was an accepted chronic HBV infection registration.

Definition of the captured population

We included persons 16 years of age or older that were diagnosed with chronic HBV infection before December 31, 2016. Persons who had a negative HBsAg or positive anti-HBs after diagnosis and before December 31, 2016 were excluded. Moreover, persons who died, emigrated, or did not have an address registered on December 31, 2016 were excluded.

As previous studies have shown questionable validity of chronic HBV diagnoses in the national patient register [13] we furthermore excluded persons who had chronic HBV infection according to the national patient register, no registration in any of the three other registers and chronic hepatitis C according to one of the four source registers. Chronic hepatitis virus infection C was defined as chronic hepatitis C diagnosis in the NPR or CDR, or positive hepatitis C virus RNA at last measurement registered in DANHEP or DANVIR.

Statistical analysis

As none of our sources included all diagnosed with chronic HBV infection, we used capture-recapture analysis to determine the size of the diagnosed population in Denmark. The estimated diagnosed population includes those registered in one of the four source registers also termed the captured population as well as the hidden diagnosed population, which is the estimated number of people who have been diagnosed but never registered in one of the four source registers. The capture-recapture methods used in this study have been described previously [6,11,14]. Capture-recapture is a type of analysis, which can be used to estimate the size of a population based on the overlap between two or more incomplete sources listing members of the population. Overlap in our context means individuals registered in more than one source. If the overlap is large, the estimated amount of people not recorded in any of the sources will be correspondingly small, and vice versa. For this analysis to be valid sources must be independent, meaning being registered in one source cannot increase or decrease the probability of being recorded in one or more of the other sources. This may not hold true for the source registers used in this analysis. For instance, all individuals who were registered in DANHEP had at least one hospital visit due to HBV, thus they may be more likely to be registered with chronic HBV infection in the NPR. We addressed this issue by performing a log linear capture-recapture analysis in which interaction between sources is allowed by inclusion of interaction terms in the model. Another assumption of the capture-recapture analysis is equal catchability, meaning that individuals in the population must have the same probability of being captured. However, the completeness of registration in the source registers used in this study may have varied over time. Moreover, Denmark is divided into five geographical regions with separate regional councils responsible for secondary health care in the regions. The probability of being registered in the source registers may also vary across these regions. To address this issue we performed the analysis stratified by age, sex, region, and year of diagnosis. For each stratum, 113 models were produced with every possible number and combinations of interactions between registers. The Akaike Information Criterion was used to choose the best fitting model. The Southern region had more consistent reporting to DANVIR leading to an increased number of cases captured in DANVIR in the Southern region, especially prior to the year 2000.

This in turn decreased overlap between registers in the Southern region. Such a decrease in overlap could cause an overestimation of the "hidden" diagnosed population. To mitigate this issue, we used a multiple indicator model to estimate the diagnosed population in the Southern region [15]. In this regression model, the capture-recapture estimates from other regions for the outcome "number of diagnosed chronic HBV infections", were used to estimate the effect of "the number captured in DANHEP", which was the independent variable. This was then used to predict the number of diagnosed chronic HBV infections in the Southern region.

The group with chronic HBV infection that were not captured by one of the four source registers consists of individuals that were diagnosed but not registered as well as individuals who are undiagnosed. As those who were not diagnosed had no chance of being registered, we assumed that the capture-recapture analysis only estimated the size of the diagnosed population. To estimate the size of the undiagnosed population, and thus the chronic HBV prevalence, we used the pregnancy screening program and assumed that the distribution of diagnosed and undiagnosed chronic HBV infections was the same among women participating in the pregnancy screening program and the rest of the population. All pregnant women have been offered HBV screening since 2005, and the participation rate is high (99.9% in 2019) [16]. Around 68.000 women are screened each year. Results from the screening program are directly reported from the performing laboratory to the communicable diseases register. We used the birth register to identify the women with chronic HBV infection in our source registers who gave birth from 2005-2016. This gave us the number of women who screened positive for HBV in the pregnancy program and thus the total number infected. We then extracted the number that were registered with chronic HBV infection in one of the four source registers, 9 months or more before the birth of their first child, which gave us the captured population. Finally, we calculated the total diagnosed population before screening by adding the "hidden" diagnosed population estimated in the capture-recapture analysis. We were then able to calculate the fraction of the infected population that was diagnosed.

$$\frac{Captured\ population + Hidden\ diagnosed\ population}{Total\ infected\ population}$$

Data management and statistical analysis were performed using STATA 14 IC [17] and GLIM4 [18].

The study was approved by the Danish Data Protection Agency (Journal no: 16/43190 and 18/52996). No further approvals were necessary for register-based studies according to Danish law.

Results

We identified 19,454 individuals with HBV in at least one of the four registers. After excluding those under 16 years of age and individuals that did not fulfil the definition for chronic HBV infection in at least one of the four registers 11,475 remained. Of these 2,938 either became HBsAg negative, died, emigrated or were without address on December 31, 2016, leaving 8,537 in the captured population. Finally, we excluded 595 who were only registered in the national patient register, had no positive HBsAg or HBVDNA registered in DANVIR and had chronic hepatitis C virus infection according to one of the four source registers. This left a final captured chronic HBV population of 7,942 persons. A flow-chart describing the selection of the captured population is presented in Figure 1.

Table 1 shows demographics of persons with chronic HBV infection in the four source registers. Overall, 4,038 (51%) were male. The median age was 44 years (range 16-91 years) and the majority were above the age of 40 years in 2016 (63%). Moreover, 5,419 (68%) had a country of origin other than Denmark. Of the five administrative regions in Denmark, most cases were identified in the Capital and the Southern region, representing 40% and 29% of the captured population, respectively. The national patient register included 5,348 (67%) of the chronic HBV cases, DANVIR had 4,932 (62%), DANHEP had 4,297 (54%) and the communicable disease register, to which notification is mandatory, included 3,289 cases constituting 41% of persons registered with chronic HBV infection. The proportion captured in the communicable disease register did not increase significantly over time (43% in 2015-16). The yearly number of new entrances

decreased over time in DANVIR and increased in the three other source registers, reflecting that DANVIR was not updated routinely (Figure 2).

The overlap between source registers is shown in figure 3. We found that 1,621 of 7,942 (20%) were registered in all four registers, while 3,152 (40%) where registered in just one of the sources. Table 2 shows results from the capture-recapture analysis which estimates the number of persons diagnosed with chronic HBV infection, including the hidden diagnosed population not captured by the four source registers. In total, we estimated that 13,530 persons were diagnosed with chronic HBV infection in Denmark by December 31, 2016, corresponding to 0.29% of the population aged 16 years or older. The hidden diagnosed population was estimated to be 5,588 cases (41%). We estimated that 5,673 (42%) individuals in the diagnosed population were under the age of 40, 3,002 (22%) individuals were 40-49 years old while 4,855 (36%) individuals where over the age of 50 years. Moreover, 7,206 (53%) were male and 6,558 (48%) lived in the Capital region. The majority (59%) was diagnosed after 2007. This trend was particularly strong in the Capital region. Of the total diagnosed population only 3,298 (24%) individuals were recorded in the communicable diseases register and 4,297 (32%) persons were recorded in DANHEP indicating that they were receiving specialized care. We found that 1,680 (74%) of the captured cases from the Southern region were registered in DANVIR, 933 corresponding to 41% of the captured cases in the Southern region were only registered in DANVIR. In the rest of the country 3,252 (57%) cases were registered in DANVIR and 726 (13%) cases were registered in DANVIR alone. Therefore, a multiple indicator model was used for the estimate in the Southern region. Had we used the capture-recapture estimate for the Southern region the estimated diagnosed population in Denmark would have been 15,172 instead of 13,530.

Overall, 2060 women gave birth and tested positive for HBV during 2005-2016. Of these 1,190 (58%) were registered 9 months or more before the birth of their first child in one of the four source registers. There was no time trend in the proportion of HBV positive women giving birth who had known chronic HBV infection prior to screening. The proportion ranged from 41-65% in individual years. We assumed the same captured proportion before screening in these women as in the women in the entire population. There were 3,904 women registered with chronic HBV infection in one of the four source registers. With our capture-recapture analysis we estimated that 6,324 women were diagnosed with chronic HBV infection.

Thus, the captured proportion among women was 0.62 (3,904/6,324). We added the hidden diagnosed proportion to the number registered prior to screening to achieve the entire diagnosed population prior to screening (1,190/0.62) which we found to be 1,919. Thus, the diagnosed proportion was 93% (1,919/2,060) among pregnant women. Assuming the same diagnostic coverage in the general population, we estimated the prevalence in Denmark, including those not yet diagnosed, to be 14,548. Figure 4 presents the cascade of care for chronic HBV infection in Denmark based on our estimate and coverage of source registers. Individuals registered in DANHEP were considered linked to specialized care.

Discussion

In this capture-recapture analysis based on four nationwide registers we estimated that 13,530 were diagnosed with chronic HBV infection on December 31, 2016. Among diagnosed individuals, 41% were not captured by any of the source registers. The chronic HBV prevalence, including undiagnosed individuals, was estimated to be 14,548 or 0.3% of the population aged 16 years or older, which was a 35% increase since 2007.

We excluded 7,861 HBV cases that did not live up to the criteria for chronic HBV infection in one of the source registers. The excluded cases were not necessarily cases of acute HBV. Cases recorded in the communicable diseases register before year 2000 may have been registered as acute, as notification of chronic HBV infection was not mandated before that time. Moreover, ICD8 codes used in the national patient register until 1993 did not specify if an HBV infection was chronic.

Contrary to our analysis in 2007 [6] we excluded persons that we believed were misdiagnosed in the national patient register. Moreover, we used a multiple indicator model to estimate the number of diagnosed chronic HBV infections in the Southern region. Both these changes to the methodology decreased the final prevalence estimate. Had we left more cases only registered in the national patient register, overall overlap between registers would have been decreased leading to a higher capture-

recapture estimate. Likewise, using the multiple indicator model for the Southern region led to a lower capture-recapture estimate. Thus, we believe that the prevalence has truly increased since 2007.

Increasing prevalence could be related to several factors. As HBV vaccination is not part of the Danish childhood vaccination program, new infections due to sexual transmission, intravenous drug use, travel or other horizontal transmission in susceptible individuals could be behind the observed increase. However, acute HBV infections are rare in Denmark [19–21], and may not fully explain the observed increase in prevalence. The majority registered with chronic HBV infection had a country of origin other than Denmark. The proportion of residents that immigrated to Denmark rose from 6.6% in 2007 to 9.5% in 2016 [22]. Thus, it is likely that immigration from areas with higher prevalence of chronic HBV infection contributed to the increasing prevalence. This is in line with previous findings from Germany, where HBsAg prevalence (3.6%) among migrants was higher than in first time blood donors, pregnant women and people who injected drugs [23]. Nonetheless, the low but increasing prevalence of HBV supports that HBV childhood vaccination should be considered in Denmark.

In Denmark, all chronic HBV care is provided by specialists in infectious diseases or gastroenterology. Therefore, it is disappointing that only 32% of individuals diagnosed with chronic HBV infection were registered in DANHEP indicating linkage to care. In a study in 589 women, who screened positive for HBsAg during pregnancy, 203 (34%) were never referred to a specialized department while 30 (5%) failed to show for an appointment [24]. Thus, steps to increase referral are likely to increase linkage to care.

As in previous studies, we found that the national HBV surveillance system, the register for communicable diseases, was far from complete [5,6]. Although notification is mandatory for the diagnosing doctor, only 41% of the captured population and 24% of the diagnosed population were registered. A previous study in Lyme neuroborreliosis, which is likewise a notifiable disease, found that automated electronic reporting from laboratories, made reporting more precise and complete compared with manual notification [25]. A similar strategy could increase the completeness of HBV surveillance in Denmark.

The overlap between registers was low with 3,152 (40%) cases registered in only one of the source registers. This was especially related to cases only registered in the national patient register and DANVIR. The low overlap had several potential causes. Firstly, suboptimal reporting to the communicable diseases register lowered overlap. Moreover, lack of referral of diagnosed individuals to specialized care would lower overlap between DANHEP and other registers. Another possible cause was the case definition that we used for cases registered in DANVIR which was wider than the definition for chronic HBV virus infection (positive HBsAg for at least 6 months). Two HBsAg tests ≥6 month apart were only available for 46% of the captured population. This may reflect that retesting is primarily applied among patients referred to specialized care. Thus, we feared that more chronic cases would have been missed if we had only accepted cases in DANVIR with positive HBsAg for at least six months. Finally, potential misdiagnoses in the national patient register could have reduced overlap between registers.

A strength of this study is that results are based on four nationwide registers. The registers include data on hospitalized patients as well as persons diagnosed in outpatient clinics or in general practice providing good representation of the target population compared with data exclusively from blood donors or hospitals. Moreover, the routine use of personal identification numbers in all public registers makes crosslinking reliable.

There are also limitations to our study. The capture-recapture analysis is based on several assumptions which our data did not fully comply with. Firstly, each registered individual must truly belong to the target population. This assumption was likely violated due to the validity of the chronic HBV diagnosis in the national patient register. A previous validation of the viral hepatitis diagnoses in the national patient register using a national HIV database as reference showed low positive predictive value for coinfection with HBV (64%) [13]. The low validity of the national patient register was also reported in our recent HCV estimate [8], and confirmed during a recent “call-in” initiative in Denmark where >90% of HCV cases only present in national patient register could not be confirmed by review of clinical records or retesting (data

not shown). To address this issue, we excluded chronic HBV infections in individuals only registered in the national patient register, with no HBsAg in DANVIR and chronic hepatitis C virus infection according to one of the four registers. Nonetheless, we suspect that a significant proportion of the remaining 935 cases only present in the national patient register (figure 3) may also be incorrectly classified. This would lead to an overestimation of the size of the diagnosed chronic HBV population. Another assumption is that the source registers are independent. As mentioned, this assumption is unlikely to hold true. We did address this issue by allowing for interaction between sources in our model, however this may not fully compensate for this weakness. A third assumption was that individuals in each stratum of our analysis had the same probability of being captured in each of the four source registries. There could be additional factors influencing catchability. For instance, it may be more challenging for persons who immigrated to navigate the heath care system decreasing the probability of them being captured in DANHEP. However, we believe we included the most important factors in our model. Too many strata would reduce power and thus precision of the model.

We estimated that 7% of all individuals with chronic HBV infection in Denmark were undiagnosed. A significant decrease compared with our 2007 estimate (33%). Although initiatives such as routine screening of pregnant women and asylum seekers may have contributed to more being diagnosed, screening was not consistently performed among other groups considered at higher risk of contracting HBV. For instance, individuals who immigrated for other reasons than the need for asylum, persons who inject drugs and MSM. Thus, the undiagnosed proportion that we found is likely underestimated. Our estimate relies on the assumption that the distribution of diagnosed and undiagnosed chronic HBV is the same among pregnant women and the entire population with chronic hepatitis B infection. However, there is reason to think that women participating in the pregnancy screening program might be more likely to be diagnosed. For example, young women could have been tested during pregnancies prior to 2005 or during pregnancies that ended in early abortions. As pregnancies terminated before the 22nd week of gestation are not included in the medical birth register, the mothers would not be considered screened in our analysis.

Moreover, health care seeking behaviors may differ in people of different age, sex, and with different routes of infection. Consequently, it is likely that the undiagnosed proportion is underestimated, leading to an underestimation of the total number of individuals with chronic HBV infection in Denmark. Had the undiagnosed proportion among pregnant women for instance been 10% higher the estimated prevalence would have been 16,301 individuals. A better estimate of the undiagnosed chronic HBV population in Denmark would require a representative seroprevalence survey in the general population, however this has never been done.

There were also limitations pertaining to the data retrieved from DANVIR. Test results are not automatically transferred to DANVIR, and since 2010 there has been a drop in test results reported to DANVIR from all regions except the Southern region. This reflects that DANVIR collects data ad hoc when needed for research projects. The lower uptake in DANVIR in recent years may have caused an underestimation of the captured population, and decreased overlap between DANVIR and the other three registers.

Conclusion

We found an estimated chronic HBV prevalence in Denmark of 14,548 individuals of whom 13,530 were diagnosed on December 31, 2016. The estimated prevalence corresponded to 0.3% of the population in Denmark and represented a 35% increase since 2007. Although the total number of infected may be underestimated, our study clearly shows that linkage to care remains a major obstacle for Denmark to fulfil the WHO goal of controlling hepatitis B by 2030. Future efforts to achieve elimination should address this. Moreover, more consistent notification to the communicable disease register is needed if it is to be used to track chronic HBV in Denmark in the future.

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Author contributions

Signe Bollerup contributed with data management, methodological decisions, interpretation of results and writing of the manuscript. Maria Wessman assisted with study design, data management, methodological

decisions and review and editing of the manuscript. Janne Fuglsang Hansen assisted with data acquisition, data management, review and editing of the manuscript. Stine Nielsen contributed to study design and review and editing of the manuscript. Gordon Hay performed the statistical analysis, assisted with methodological decisions and reviewed and edited the manuscript. Susan Cowan, Henrik Krarup, Lars Omland, Peter Jepsen and Nina Weis provided data and reviewed and edited the manuscript. Peer Brehm Christensen managed the project, and contributed to the study design, data acquisition, methodological decisions, interpretation of results, manuscript production and editing.

Ethics approval

The study was approved by the Danish Data Protection Agency (Journal no: 16/43190 and 18/52996). No further approvals were necessary for register-based studies according to Danish law.

Data availability statement

The dataset for the study is available from Zenodo.org. DOI: 10.5281/zenodo.5824584.

Table 1: Characteristics of persons registered with chronic hepatitis B virus infection in the four source registers on December 31, 2016.

	DANVIR		Communicable disease register		NPR		DANHEP		TOTAL	
N	4,932	62%	3,289	41%	5,348	67%	4,297	54%	7,942	100%
Male	2,455	50%	1,386	42%	2,619	49%	2,132	50%	4,038	51%
Age										
<40	1,650	33%	1,579	48%	2,202	41%	1,834	43%	2,965	37%
40-49	1,552	31%	932	28%	1,531	29%	1,244	29%	2,307	29%
>50	1,730	35%	778	24%	1,615	30%	1,239	29%	2,671	34%
Region										
North	301	6%	139	4%	361	7%	326	8%	474	6%
Central	914	19%	570	17%	1,048	20%	964	22%	1,347	17%
South	1,680	34%	746	23%	1,103	21%	952	22%	2,274	29%

Zealand	267	5%	364	11%	498	9%	344	8%	680	9%
Capital region	1,770	36%	1,470	45%	2,338	44%	1,711	40%	3,168	40%
Year of inclusion										
<2000	1,125	23%	161	5%	488	9%	276	6%	1,562	20%
2000-2007	2,605	53%	1,194	36%	1,499	28%	1,317	31%	3,031	38%
2008-2016	1,202	24%	1,934	59%	3,361	63%	2,704	63%	3,350	42%

DANHEP: Clinical register, DANVIR: Laboratory register, NPR: National Patient register.

Table 2: Capture-recapture estimate of the prevalence of diagnosed chronic hepatitis B virus infection on December 31, 2016.

	Region											
	North		**Central**		**South**		**Zealand**		**Copenhagen**		**Total**	
Proportion of estimate for Denmark (%)	5		17		22		8		48		100	**Population prevalence %**
Prevalence (%) Among population ≥16 years of age	0.14		0.21		0.29		0.16		0.44		0.29	
	N	%	n	%	n	%	N	%	n	%	N	
Age												
<40	272	41	827	36	1,257	43	455	40	2,862	44	5,673	0.33
40-49	168	26	852	38	577	20	260	23	1,145	17	3,002	0.38
≥50	220	33	589	26	1,084	37	411	37	2,551	39	4,855	0.22
Sex												
Male	340	52	1,271	56	1,579	54	579	51	3,437	52	7,206	0.31
Female	320	48	997	44	1,339	46	547	49	3,121	48	6,324	0.26
Entrance in Register												
2000 or earlier	104	16	222	10	546	19	125	11	603	9	1,600	
2000 - 2007	174	26	916	40	821	28	395	35	1,671	25	3,977	
After 2007	382	58	1,130	50	1,551	53	606	54	4,284	65	7,953	
Total	660	5	2,268	17	2,918	22	1,126	8	6,558	48	13,530	0.29

Figure 1: Flow diagram of selection of the captured population with chronic hepatitis B virus infection on December 31, 2016.

HBsAg: hepatitis B surface antigen, NPR: National patient register.

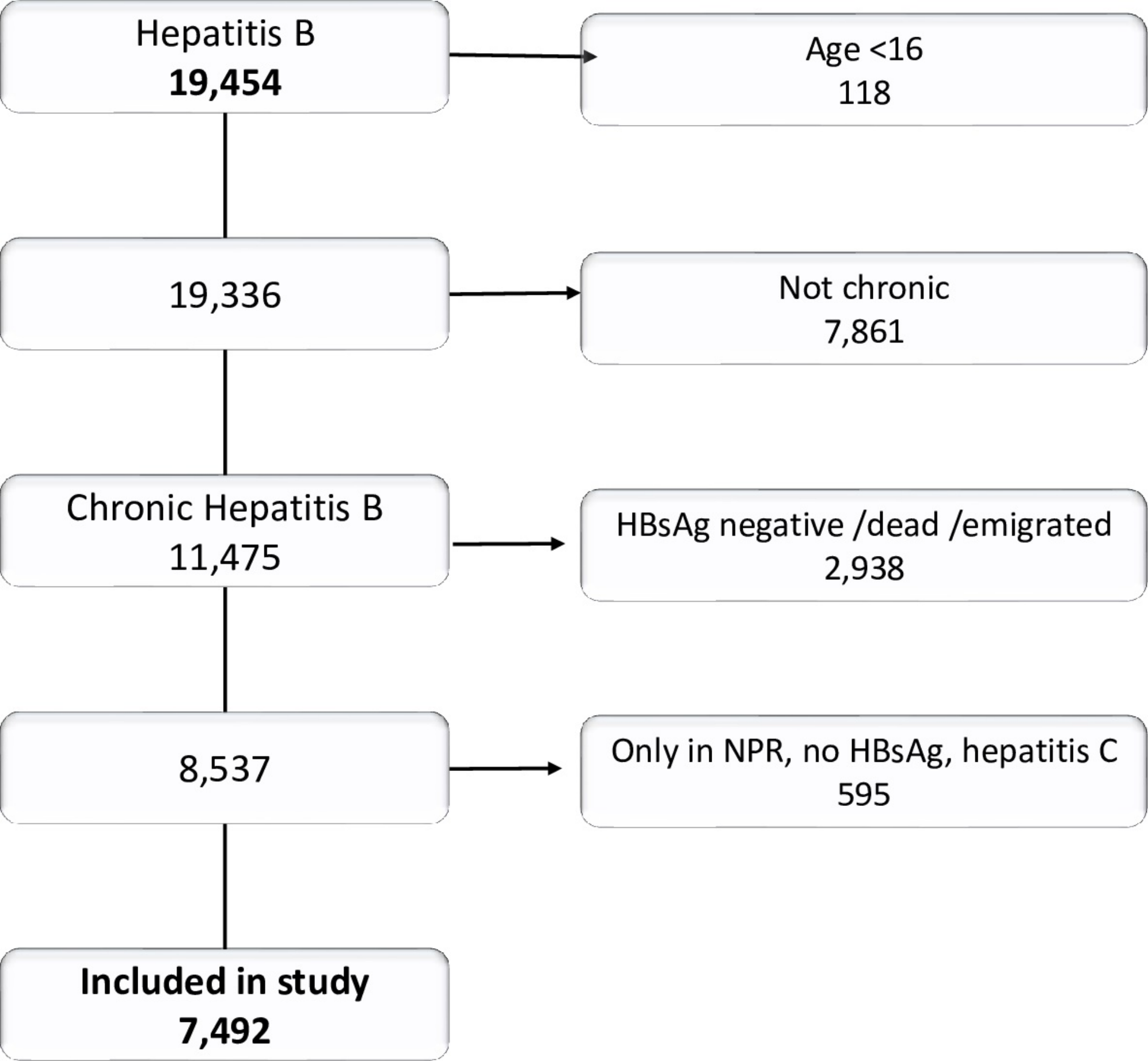
Figure 2: Chronic hepatitis B cases registered per year in the four source registers.

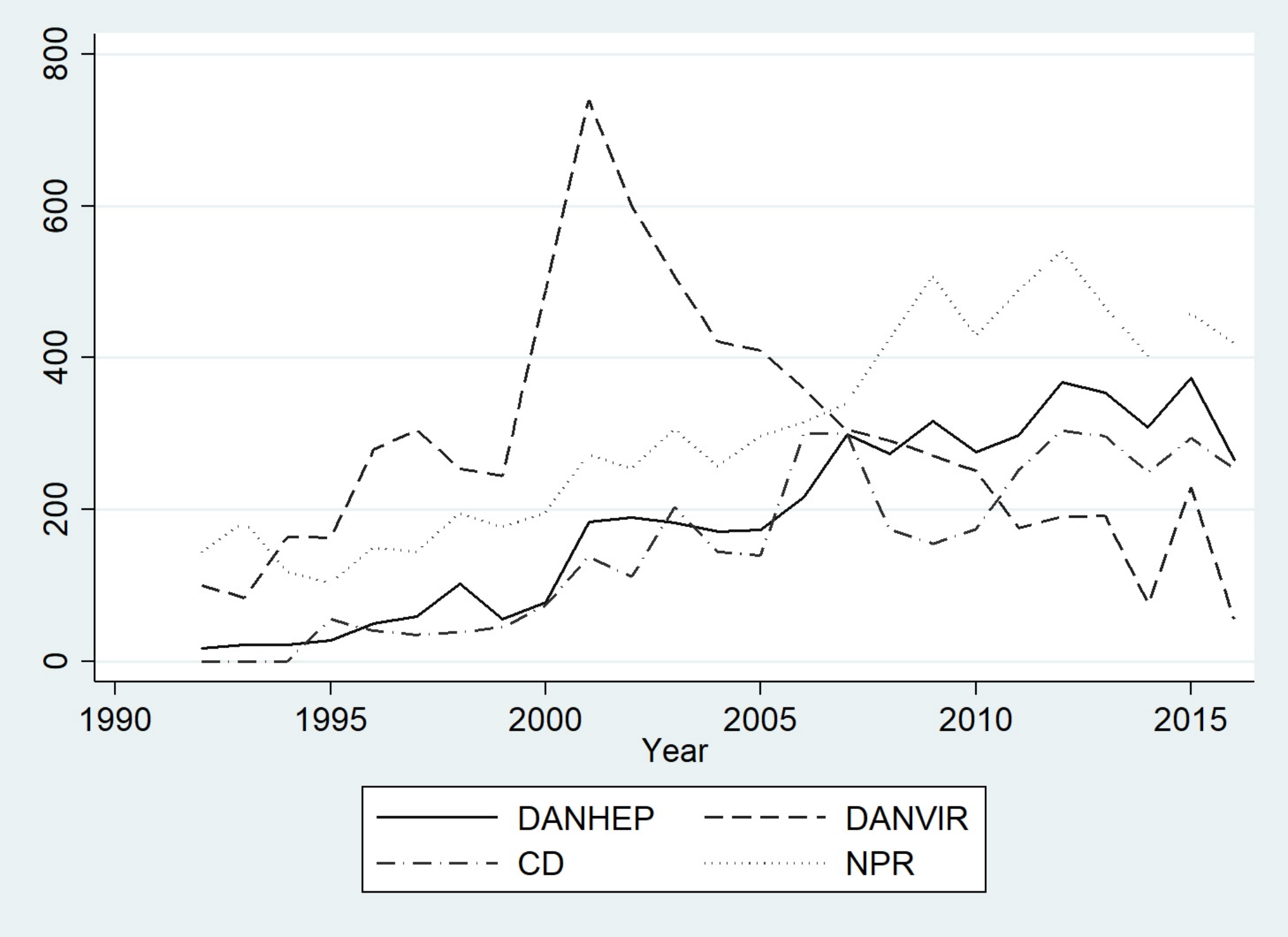
CD: Communicable Disease Register, DANHEP: Clinical register, DANVIR: Laboratory register, NPR: National Patient Register.

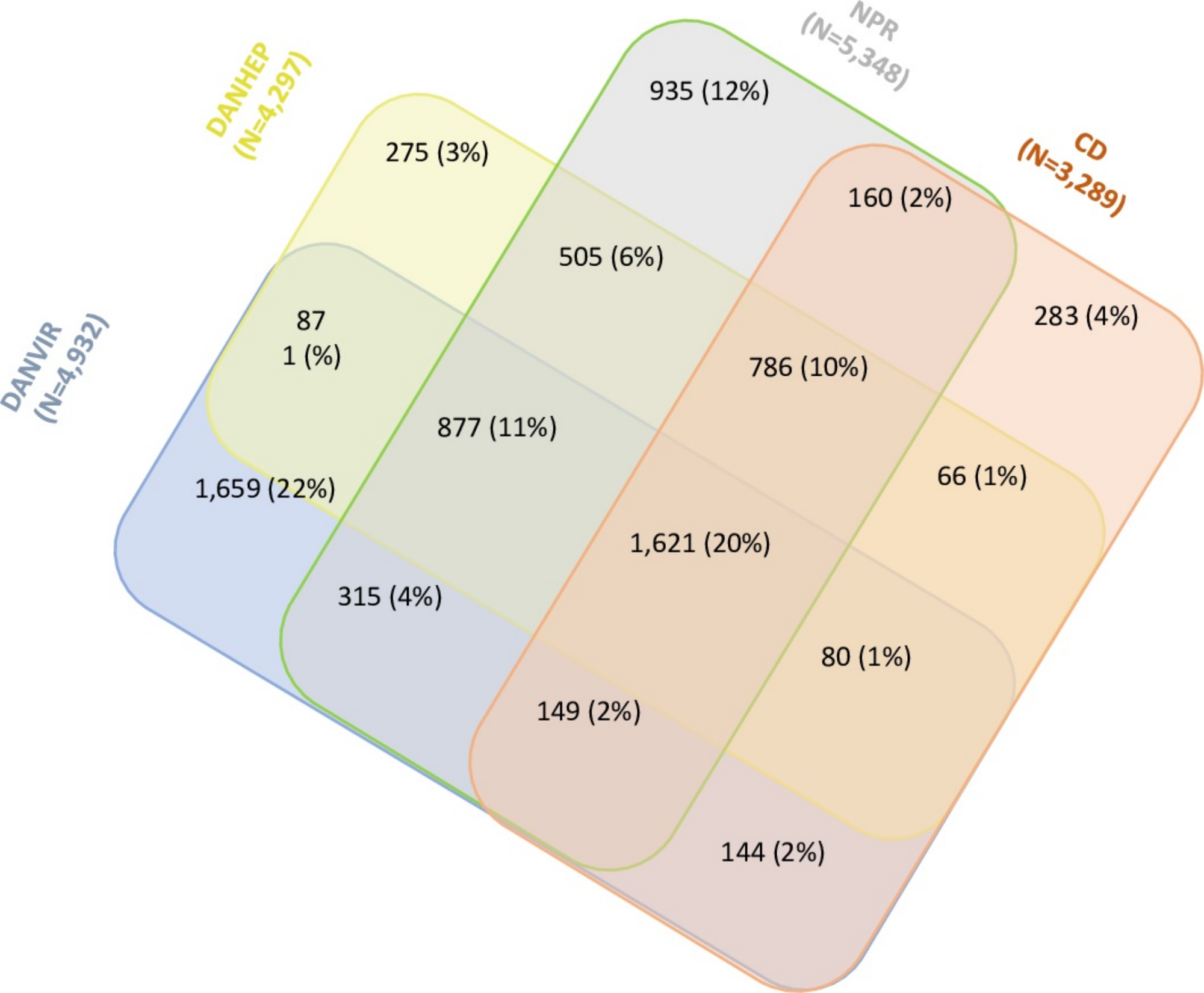
Figure 3: Overlap between the four source registers

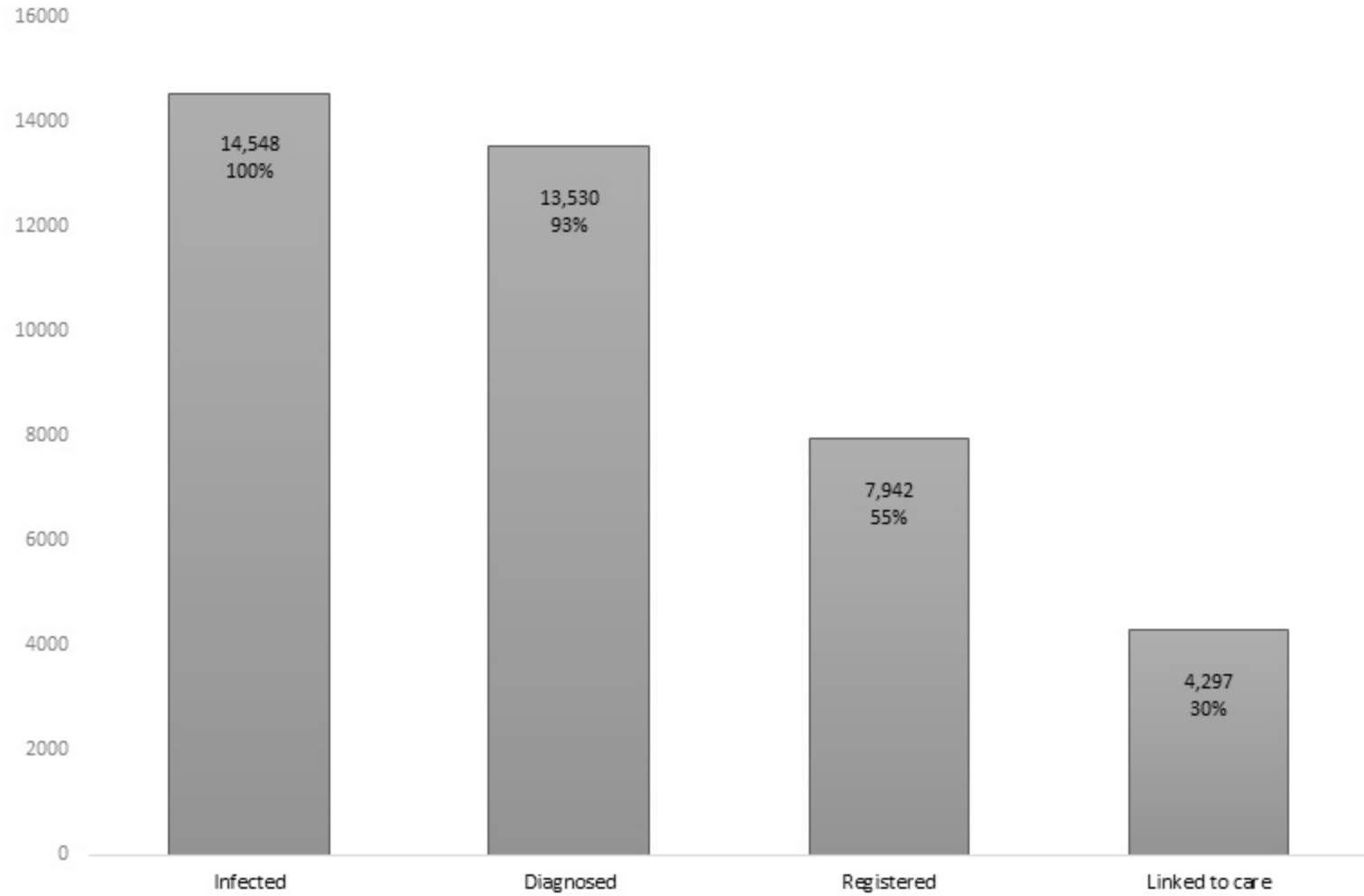
CD: Communicable Disease Register, DANHEP: Clinical register, DANVIR: Laboratory register, NPR: National Patient Register.

Figure 4: Estimated cascade of care for chronic hepatitis B virus infection in Denmark on December 31, 2016.


Hepatitis B
19,454
Age <16
118
19,336
Not chronic
7,861
Chronic Hepatitis B
11,475
HBsAg negative /dead /emigrated
2,938
8,537
Only in NPR, no HBsAg, hepatitis C
595
Included in study
7,492


800
600
400
200
0
1990
1995
2000
2005
2010
2015
Year
DANHEP
DANVIR
CD
NPR


DANHEP
(N=4,297)
NPR
(N=5,348)
CD
(N=3,289)
DANVIR
(N=4,932)
275 (3%)
935 (12%)
160 (2%)
505 (6%)
87
1 (%)
283 (4%)
786 (10%)
877 (11%)
66 (1%)
1,659 (22%)
1,621 (20%)
315 (4%)
80 (1%)
149 (2%)
144 (2%)


16000
14000
12000
10000
8000
6000
4000
2000
0
14,548
100%
13,530
93%
7,942
55%
4,297
30%
Infected
Diagnosed
Registered
Linked to care