Risk assessment of Hepatitis A based on hepatitis A IgG testing

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Introduction

The cost of vaccination is in our experience a main issue for immigrants from Asia and Africa visiting their home countries. To avoid unnecessary expensive hepatitis A vaccine we have at our clinic routinely since 1999 tested vaccine candidates who have grown up in countries that are highly endemic for hepatitis A for hepatitis A IgG antibodies.

Data and Methods

A total of 369 patients at Oslo Travel Clinic, Norway were tested for presence of Hepatitis A IgG by Abbott AxSYM HAVAB((Abbott Laboratories, Diagnostics Divsion, Abbott Park, IL 60064, U.S.A.) The patients had all spent a substantial part of their life outside of Norway, and all but 22 were born abroad. In addition to the test, patients were asked to provide the durations of their stay outside of Norway, and the countries in which they had resided. Finally, the gender of the patient was recorded (Table 1). In the data set 359 patients had complete data and were retained for analysis.

Since the purpose of this paper is to estimate how long a person must have resided in a country for us to be reasonably certain that he or she will be test positive for Hepatitis A IgG, the estimation problem can be seen as falling within the general class of survival problems. In this case the data can be considered as current status data (Diamond and McDonald 1991; Shiboski 1999). These are data where only the duration of exposure and the status at the end of the exposure are known. Formally, we want to estimate a time to occurrence (testing positive) V, given a vector $\boldsymbol{Z}$ of covariates. The data consist of the random variables V,$\boldsymbol{Z}$ and Y, where Y is a binary outcome variable so that for a given individual Y_i

$$Y_i = \begin{cases} 1 \, if \;\; V_i \le T_i \\ 0 \, if \;\; V_i > T_i \end{cases}$$

Thus, in classical survival analysis terminology the data are doubly censored in that they are right censored when $V_i > T_i$ and left censored otherwise.

Despite the lack of information in the data it can be shown that Y_i can be estimated in a generalized linear models framework (McCullagh and Nelder 1989) and in particular as indicated above as a binary outcome model (Shiboski 1999).

We will focus on the proportional hazards model, where the covariates are seen to influence a baseline hazards function under the assumption that for every value of v, i.e. on every point of the survival curve, there is a fixed factor with which to multiply a baseline hazard in order to obtain the hazard given a particular value of a explanatory variable (Note: we are here talking about 'survival' in statistical terms, which here represents the status of not having hepatitis A antibodies, and 'hazard' refers to the conditional probability of obtaining a positive test in a time interval, given having tested negative up to the beginning of the interval, although having had hepatitis A would in this case be a favourable outcome of the test). Details of theory and estimation are given in Shiboski 1999. The estimates were calculated using a function developed in Fortran and Splus by

Stephen Shiboski and adapted for use under Splus 4.5 by the third author. Tabulations were produced using SPSS for Windows 12. We considered the duration of exposure measured by the number of years spent outside Norway. A limitation of the data is that few patients had very short durations with only 8.9 percent with less than 5 years. This leads to relatively poor precision of the estimates for very short durations.

Results

The data show a balanced gender distribution except for patients from Eastern Europe and Asia outside of the Indian subcontinent where there is a preponderance of women, most likely due to marriage migration into Norway from these areas (table 1). The arithmetic mean durations of exposure were generally around 17 to 21 years, but with the African durations shorter (14 years) and the Eastern European higher (23 years overall, and as much as 33 years for men).

Overall 80 percent of the patients were found to be Hepatitis A IgG positive, while higher percentages were recorded for Africans (85 percent), MENA (Middle East and North Africa) (90 percent) and lower for those from Eastern Europe (65 percent). No obvious pattern by gender in presence of Hepatitis A IgG can be discerned.

The proportional hazards model provides similar results. Exposure in Africa, Middle East North Africa increases the hazard significantly, while exposure in Asia is not significant compared to the baseline hazard. Being a woman reduces the hazard of being Hepatitis A IgG positive.

The expected percent Hepatitis A IgG negative shown in Table 3 show that for most regions there are few that are negative beyond five years of exposure. As can be seen from A Figure 1, the survival curve drops sharply the first years of exposure and then flattens out at low levels.

Discussion

Cost effectiveness of pre travel hepatitis A IgG testing has been calculated by Tormans et al. (Fig 2.) In Norway one dose of hepatitis A vaccine costs about 45 US$, and a test for hepatitis A IgG costs about 11 US$. As two doses of vaccine would be needed, testing may be cost effective if the *à priori* probability of being positive is more than 10-15%. However, for many travellers, the advantage of finishing the consultation at once, would weigh more than the possible saving of costs, as one would have to take risk of having to return one more time before the travel. In the immigrant population, with a high probability of being immune, and often poor economic resources testing would be the best option.

A previous study (Hasle and Espinoza 1994) showed that hepatitis A did not occur in Oslo 1989-1994 among adult people with Muslim/Pakistani names. In the present material and in other unpublished serologic tests in Oslo we have not found one single person who have lived more than nine years in Pakistan who have been hepatitis IgG antibody negative. People from Pakistan, who left their country as adults, were considered as naturally immune without being tested before travel, and were therefore not included in the study. The observed gender difference is not in accordance with the generally accepted fact that hepatitis A attacks males and females equally, and may be a result of a bias in our material, where females in average had stayed 27 years while males had stayed 17 years in the high endemic country.

Conclusion

The material is at present far too small to be used as an assessment of risk of contracting hepatitis A per time unit in each country. It seems obvious that pre travel testing is cost effective when hepatitis A vaccine may be omitted as a consequence of the test. In most cases it will be cost effective when we have to give one dose before departure, and then omit the second dose if the test is positive for hepatitis A antibodies. When the *a priori* chance of being naturally immune is low the vaccine should be given without testing, and when the *a priori* chance of being positive is very high (>85%?) it may be justifiable to omit both the test and the vaccine.

Acknowledgments

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References

Diamond, ID and JW MacDonald 1991"The Analysis of Current Status Data" in J. Trussel, R. Hankinson and J.Tilton [eds] Demographic Applications of Event History Analysis. Oxford: Oxford University Press.

Hasle G and Espinoza R: Hepatitt A i Oslo. Tidsskr Nor Lægeforen 1995;115:215-7 (Norwegian).

Hasle G and Espinoza R:Hepatitt A in Oslo. Poster 129. Fourth International Conference of Travel Medicine. April 23-27. 1995. Acapulco, Mexico

McCullagh, P and JA Nelder, 1989, Generalized Linear Models, 2nd Ed, New York: Chapman and Hall.

Shiboski,1998, SC. **"**Generalized additive models for current status data" Lifetime Data Anal. 1998;4(1):29-50.

Tormans G, Van Damme P, Van Doorslaer E: Recommendations for prevention of Hepatitis A Based on a Cost-Effectiveness Analysis. J Trav Med1:127-135, 1994.

Tables

Table 1: Duration of exposure, gender and Hepatitis A IgG status by world regions

	Duration of exposure (mean years)			Gender		Percent positive Hepatitis IgG			
	Men	Women	Total	Men	Women	Men	Women	Total	Number
Africa	14.9	13.9	14.4	50.6	49.4	86.0	83.3	84.7	85
Middle East North Africa	18.9	19.9	19.3	59.2	40.8	86.2	95.0	89.8	49
Latin America	17.5	21.5	19.6	47.8	52.2	81.8	66.7	73.9	23
Indian subcontinent	18.8	16.8	17.8	47.6	52.4	83.3	77.3	80.2	126
Other Asia	14.1	18.2	16.9	30.8	69.2	68.8	72.2	71.2	52
Western Europe .		21.0	21.0	-	100.0		80.0	80.0	5
Eastern Europe	33.0	19.6	22.7	23.5	76.5	50.0	69.2	64.7	17
Other	24.0	9.0	16.5	50.0	50.0	100.0		50.0	2
Total	17.6	17.3	17.4	45.7	54.3			79.9	359

Table 2: Proportional hazards current status regression of Hepatitis A IgG antibody

Covariate	Coefficient	Standard error	Hazard ratio	Lower 95% confidence interval	Higher 95% confidence interval
Gender	-0.084	0.019	0.920	0.885	0.955
India	0.389	0.051	1.475	1.335	1.630
Africa	0.664	0.060	1.943	1.725	2.187
Asia	0.129	0.070	1.138	0.992	1.304
Middle East North Africa	0.634	0.074	1.886	1.632	2.180

Table 3: Expected percent Hepatitis A IgG Negative by region and gender

	Men			Women		
	5 year	10 years	15 years	5 year	10 years	15 years
India	15	15	15	39	29	0
Africa	23	5	5	33	5	5
Asia	0	0	0	10	10	10
Middle East North Africa	0	0	0	0	0	0
All	16	16	16	36	23	23

Figures

Figure 1: Expected (baseline) probability of being Hepatitis A IgG negative by duration of exposure by gender

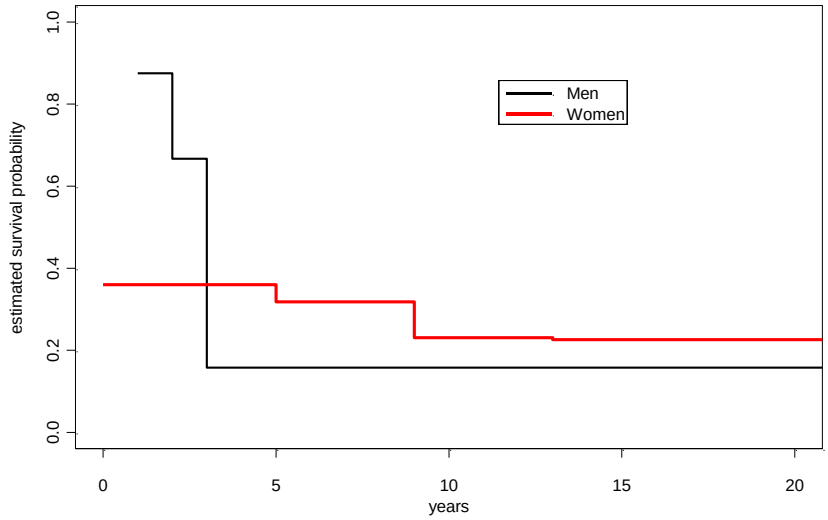

Figure 2.

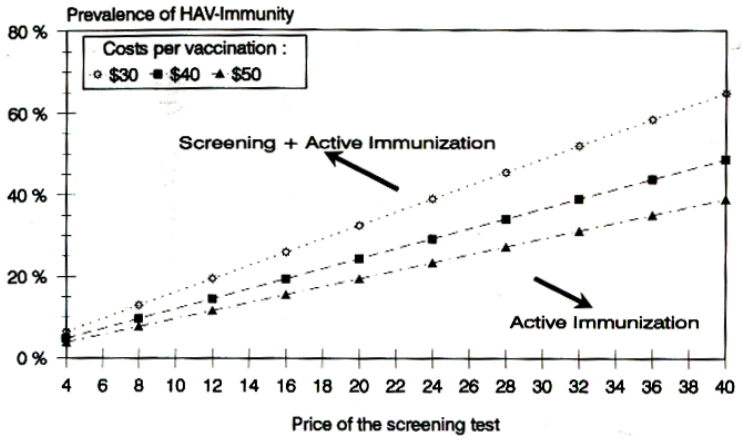

Figure 3 For three different vaccination costs, the dotted threshold lines show the total of all combinations of the cost of the screening test and the prevalence rates of HAV-immunity at which both strategies are equally cost effective. For combinations above the lines screening plus vaccination is more cost effective than immediate vaccination and vice versa.