cancer. The large joint cohort size and five independent country specific observations in this joint Nordic study reduce the possibility of chance findings, and carefully registered incidence data help to avoid artefacts possibly included in the mortality statistics. Because of the complete population registration systems in all Nordic countries and accurate computerised record linkage procedures, the standardised incidence ratio estimates in this study are not prone to bias attributable to incomplete follow up or failures in record linkages.

Because our cohort included most of the cockpit crew ever certified in the Nordic countries, this study can be considered to have maximum potential to study cancer incidence among pilots. We were able to assess cancer risk by level of exposure, take into account characteristics of cancer (for example, subtypes of leukaemia, tumour latency), and estimate independent effects of exposure, age, and time period of the diagnosis in a way that has not been meaningful in small national settings. Apart from skin cancers, male Nordic pilots seem to have a pattern of cancer typical of that of high social class men in the Nordic countries. Our study shows a need for detailed studies focusing on possible work related factors involved in the evidently raised risk of skin cancer and the suggestive dose-response patterns in prostate cancer.

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Competing interests: RA has been employed by Finnair as an airline pilot since 1988 and has shares in Finnair. He is also an active member of the Finnish Pilots' Association and has been reimbursed by the association for attending medical symposiums and conducting scientific research. HE has worked as an medical consultant for Scandinavian Airlines. The other authors have no connections to airline companies.

What is already known on this topic

Airline pilots are occupationally exposed to cosmic radiation and other potentially carcinogenic elements

In the studies published so far, dose-response patterns have not been characterised

What this study adds

No marked risk of cancer attributable to cosmic radiation is observed in airline pilots

A threefold excess of skin cancers is seen among pilots with longer careers, but the influence of recreational exposure to ultraviolet light cannot be quantified

A slight increase in risk of prostate cancer with increasing number of long haul flights suggests a need for more studies on the effects of circadian hormonal disturbances

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Observational study of vaccine efficacy 14 years after trial of hepatitis B vaccination in Gambian children

ELPS

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Abstract

Objective To determine the duration of protection from hepatitis B vaccine given in infancy and early childhood.

Design Cross sectional serological study of hepatitis B virus infection in children of various ages 14 years after the start of a trial of vaccination regimens.

Setting Two villages in the Gambia.

Participants Children and adolescents given hepatitis B vaccine in infancy or early childhood: 232 were aged 1-5 years, 225 aged 5-9 years, 220 aged 10-14 years, and 175 aged 15-19 years.

Main outcome measures Vaccine efficacy against infection and against chronic infection in the different age groups.

Results Vaccine efficacy against chronic hepatitis B virus carriage was 94% (95% confidence interval 89% to 97%), which did not vary significantly between the age groups. Efficacy against infection was 80% (76% to 84%). This was significantly lower in the oldest age group (65%, 56 to 73). Of the uninfected participants in this age group, 36% had no detectable hepatitis B virus surface antibody. Time since vaccination and a low peak antibody response were the most powerful risk factors for breakthrough infection ($P < 0.001$ in each case). Low peak antibody response was also a risk factor for chronic carriage (odds ratio 95, 19 to 466).

Conclusions Children vaccinated in infancy are at increased risk of hepatitis B virus infection in the late teens. The risk of chronic carriage after sexual exposure needs further assessment to determine if booster vaccines are necessary.

Introduction

Chronic infection with hepatitis B virus is a leading cause of death from cancer in Africa; a quarter of the 60 million carriers die either of primary hepatocellular carcinoma or cirrhosis of the liver.[1 2] However,

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Table 1 Vaccine efficacy in 1998 against chronic carriage of hepatitis B virus and breakthrough infection overall by village and by age group

	Chronic carriage		Breakthrough infection	
	No infected in vaccine *v* control	Vaccine efficacy (%) (95% CI)	No infected in vaccine *v* control	Vaccine efficacy (%) (95% CI)
Overall	10/855 *v* 191/931	94 (89 to 97)	102/847 *v* 564/929	80 (76 to 84)
Keneba	6/628 *v* 83/622	93 (84 to 97)	68/624 *v* 302/620	78 (72 to 82)
Manduar	4/227 *v* 108/309	95 (87 to 98)	34/223 *v* 246/309	81 (74 to 86)
<5 years (group 6)	3/235 *v* 68/354	93 (79 to 98)	14/232 *v* 140/354	85 (74 to 91)
5-9 years (group 5)	0/225 *v* 66/309	100	10/224 *v* 309/509	93 (85 to 96)
10-14 years (group 4)	2/220 *v* 39/191	96 (82 to 99)	33/220 *v* 156/190	82 (75 to 87)
≥15 years (groups 1, 2, 3)	5/175 *v* 18/77	88 (68 to 95)	53/171 *v* 68/76	65 (56 to 73)

although hepatitis B vaccination is the simplest and most effective intervention to prevent mortality in adults both globally and in Africa,[2] only one country in west Africa and two in southern Africa have a continuing vaccination programme.[3] We investigated vaccine efficacy against infection and protection against chronic carriage after 14 years.

Methods

The demographic and medical background of the villages of Keneba and Manduar, which in 1998 had populations of 1474 and 607 respectively, has been described previously.[4] Surveys of hepatitis B virus infections in these villages took place in 1973, 1980,[4] 1984,[5] 1989,[6] and 1993[7] and from November 1998 to March 1999. At the time of the third survey in November 1984 all children under the age of 5 years who were seronegative for hepatitis B virus infection were vaccinated. These children were assigned randomly to receive plasma derived vaccine against hepatitis B virus according to one of three vaccination regimens (groups 1 to 3; see bmj.com for details). Subsequent vaccination of newborn infants has continued with four doses of various vaccines given intramuscularly. Children were also randomly assigned to one of three regimens (groups 4 to 6).

Concentrations of antibody to hepatitis B virus surface antigen (anti-HBsAg) were measured two months after vaccination (peak antibody), and this and other tests for hepatitis B virus core antibody (anti-HBc) and hepatitis B virus surface antigen (HBsAg) were carried out at each survey.[7]

Table 2 Independent factors associated with core antibody breakthrough infection

Variable	No (%) of breakthrough infections	Adjusted odds ratio (95% CI)	P value for variable
Vaccination group (median time (years) since vaccination):			
Group 1 (13.6)	21/52 (40)	8.9 (3.8 to 20.8)	0.0001
Group 2 (13.6)	18/56 (32)	9.0 (3.8 to 21.1)	
Group 3 (13.6)	14/63 (22)	7.7 (3.2 to 18.5)	
Group 4 (10.7)	25/220 (11)	3.3 (1.6 to 7.1)	
Group 5 (6.3)	9/202 (4)	1.3 (0.5 to 3.3)	
Group 6 (2.1)	15/254 (6)	1.0	
Sex:			
Male	60/426 (14)	1.6 (1.0 to 2.6)	0.04
Female	42/421 (10)	1.0	
Peak antibody (mIU/ml):			
<10	19/39 (49)	11.9 (4.9 to 28.8)	0.0001
10-99	12/58 (21)	3.4 (1.5 to 7.8)	
100-999	36/224 (16)	1.8 (1.0 to 3.2)	
≥1000	33/449 (7)	1.0	
Village:			
Manduar	34/223 (15)	1.8 (1.1 to 3.0)	0.03
Keneba	68/624 (11)	1.0	

Results

By the time of the 1998 survey 1041 young people (833 aged 0-14 years, 208 aged ≥15 years) had been vaccinated in the two villages. We excluded from the study 29 infants who were below 1 year of age and 23 children who had received two or fewer doses of vaccine, leaving 989 children. Of these 989, 856 gave a blood sample, 64 refused to take part, 33 had died, and 36 could not be traced; coverage ranged from 94% for children aged 1-4 years to 81% for those between 15 and 19 years.

Effect of vaccination on pattern of infection

At the start of vaccination Manduar had a much higher prevalence of hepatitis B virus infection and HBsAg carriage compared with Keneba. Between 1984 and 1998 vaccination dramatically reduced the prevalence of hepatitis B virus infection in children from 48% (302/620) to 11% (68/624) in Keneba and from 80% (246/309) to 15% (34/223) in Manduar. The corresponding changes in HBsAg carriage rates were from 13% (83/622) to 1% (6/628) in Keneba and from 35% (108/309) to 2% (4/227) in Manduar.

Vaccine efficacy by village and age

Overall, crude vaccine efficacy against HBsAg carriage was 94% (95% confidence interval 89% to 97%), which did not vary significantly between villages or by age group (table 1). Overall crude vaccine efficacy against infection was 80% (76% to 84%), which did not vary between villages but differed according to age group, being significantly lower among those aged ≥15 years compared with any of the other younger age categories ($P<0.001$). After we adjusted for age and village, the overall vaccine efficacy against carriage was 94% (89% to 97%) and against infection was 82% (78% to 85%).

Duration of response and breakthrough infections in children immunised in 1984

The participants had a median age in 1998 of 16.2 years (range 14.2-21.7 years) and had been followed up for a median of 13.8 (13.5-14.1) years. In each of the groups, which had significantly different peak antibody responses in 1985 ($P<0.0001$), antibody decayed in a similar and regular exponential manner with time. The proportion of uninfected participants with undetectable antibody concentrations (<10 mIU/ml) differed between the groups (P=0.001) and increased with time ($P<0.0001$) (see bmj.com).

The proportion of breakthrough infections and the cumulative proportion of breakthrough infections (consisting of current infections and past infections that were no longer detectable) also increased with time ($P<0.0001$ in both cases), but neither of these proportions differed significantly between the groups. By 1998, 64 of the 171 (37%) vaccinated participants had been infected, and of the 111 uninfected participants, 40 (36%) had undetectable concentrations of antibody.

Vaccine efficacy against infection was 49% (28% to 64%), 36% (5% to 57%), and 92% (57% to 100%) for vaccination regimen groups 1, 2, and 3, respectively ($P<0.01$ for comparison between group 1 or 2 and 3). In 1998 one of 54, 4 of 57, and none of 64 participants in groups 1, 2, and 3 were chronic carriers of HBsAg. Two of the chronic carriers were infected within a year of vaccination; the three others were infected five or more years later. Vaccine efficacy against chronic carriage was 91% (37% to 99%), 66% (11% to 87%), and 100% for groups 1, 2, and 3, respectively.

Breakthrough infections and chronic carriage according to peak antibody responses

The number of breakthrough infections was related to vaccination group (P=0.01) and to the peak antibody concentration (P=0.001) (see table 3 in full version on bmj.com).Those with an undetectable response (equivalent to <10 mIU/ml) had six times the chance of infection compared with those with high responses (>999 mIU/ml). More importantly, participants whose peak antibody response was <10 mIU/ml were 75 times more likely to become chronic carriers than those with responses ≥ 10 mIU/ml ($P<0.0001$). Seven out of the 10 chronic carriers, all of whom had a peak antibody response of less than 10 mIU/ml, were infected before the age of 5 years.

Predictors of breakthrough infections and chronic carriage

Time since vaccination and peak antibody concentrations were strongly associated with breakthrough infection in a logistic regression model; sex and village had a significant but lesser effect (table 2). Dose (three or four) was not significant, neither was route of administration.

The only factor associated with chronic carriage of hepatitis B virus was a peak response of <10 mIU/ml (8/39 (21%) versus 2/731 (0.3%) children with a higher response (odds ratio 95, 95% confidence interval 19 to 466)).

Discussion

Natural boosting and immunity

The role of natural boosting in maintaining immunity in highly endemic settings is not clear. In our study antibody concentrations in uninfected older teenagers stabilised over the previous four years, perhaps as a result of increased exposure by the sexual route. In a larger cohort of Gambian people vaccinated in infancy, we have noted transient rises in antibody concentrations, which may be due to transient infections and which probably boost both cellular and humoral immunity.[9 10] The role, if any, that sexual exposure plays in maintaining and boosting immunity remains to be defined and at present there are insufficient data to decide if a booster dose would be useful in teenagers in highly endemic areas where 15% of sexual partners may be chronic carriers of hepatitis B virus.[4 11] In an area of low endemicity teenagers vaccinated in infancy may lose immunity because of lack of exposure, and a booster dose may be necessary at the onset of sexual maturity. In this setting it may be more sensible to deliver the primary course of vaccine in adolescence.

What is already known on this topic

An expert panel has declared that booster immunisations are not needed for lifelong immunity to hepatitis B

The evidence for maintenance of immunity in teenagers after vaccination in infancy is slender

The risk of hepatitis B virus infection is increased by sexual exposure

What this study adds

Teenagers vaccinated in infancy have low concentrations of antibody to hepatitis B surface antigen

Even though breakthrough infections are common at this age, protection against chronic infections with hepatitis B virus may be maintained

Risk factors for breakthrough infection

Independent risk factors associated with breakthrough infection were sex, village, time since vaccination, and peak antibody response. Boys and young men had a higher risk, as did people living in Manduar, which before vaccination had a remarkably high rate of infection of 71% in young children over a four year period.[5] As age and type of vaccine were directly linked in groups 4, 5, and 6 we were not able to analyse these effects separately for the whole dataset. However, in participants in groups 1, 2, and 3, who were simultaneously given different doses by different routes, time since vaccination seemed to be a major determinant. Breakthrough infections and chronic carriage were clearly and strongly related to peak antibody concentrations. Thus half of the children who failed to produce detectable concentrations of antibody became infected, most within the first five years after vaccination, and of those infected nearly half became chronic carriers. However as the numbers were small and as vaccines, dose, and routes of administration varied we were not able to assess formally which of these factors were the most important determinants of breakthrough infections resulting in chronic carriage of hepatitis B virus.

Other long term follow up studies

Few of the follow up studies of infants or young children vaccinated against hepatitis B virus have lasted longer than 10 years.[8 12–14] The longest was in China, where 52 of the original 477 children (11%) were followed for 15 years: half had detectable concentrations of anti-HBsAg, and vaccine efficacy was 87% for chronic carriage and 86% for infection.[14] This small study with a large dropout rate formed the basis for a recent consensus statement that no hepatitis B virus booster was required for 15 years after primary vaccination.[15] However as the age at first sexual intercourse may be higher in China than in Africa the findings may not be generally applicable to other groups who start sexual activity earlier.[16]

In conclusion, our long term study of infant hepatitis B virus vaccination in infancy in a highly endemic country showed that vaccine efficacy against infection waned with time but efficacy against chronic infection remained high over 14 years. However, the numbers involved are relatively small and a larger study of efficacy during adolescence is necessary before we conclude that a booster dose is not needed[15] before the onset of sexual activity. In Africa and elsewhere, the risk of infection and of chronic carriage might be increased by the presence of other sexually transmitted infections, as is the case for HIV-1.[17]

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Type specific persistence of high risk human papillomavirus (HPV) as indicator of high grade cervical squamous intraepithelial lesions in young women: population based prospective follow up study

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Abstract

Objectives To investigate the role of human papillomavirus (HPV) in the development of cervical neoplasia in women with no previous cervical cytological abnormalities; whether the presence of virus DNA predicts development of squamous intraepithelial lesion; and whether the risk of incident squamous intraepithelial lesions differs with repeated detection of the same HPV type versus repeated detection of different types.

Design Population based prospective cohort study.

Setting General population in Copenhagen, Denmark.

Participants 10 758 women aged 20-29 years followed up for development of cervical cytological abnormalities; 370 incident cases were detected (40 with atypical squamous cells of undetermined significance, 165 with low grade squamous intraepithelial lesions, 165 with high grade squamous intraepithelial lesions).

Main outcome measures Results of cervical smear tests and cervical swabs at enrolment and at the second examination about two years later.

Results Compared with women who were negative for human papillomavirus at enrolment, those with positive results had a significantly increased risk at follow up of having atypical cells (odds ratio 3.2, 95% confidence interval 1.3 to 7.9), low grade lesions (7.5, 4.8 to 11.7), or high grade lesions (25.8, 15.3 to 43.6). Similarly, women who were positive for HPV at the second examination had a strongly increased risk of low (34.3, 17.6 to 67.0) and high grade lesions (60.7, 25.5 to 144.0). For high grade lesions the risk was strongly increased if the same virus type was present at both examinations (813.0, 168.2 to 3229.2).

Conclusions Infection with human papillomavirus precedes the development of low and high grade squamous intraepithelial lesions. For high grade lesions the risk is greatest in women positive for the same type of HPV on repeated testing.

Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted viruses. Although most infections are transient, the potential health implications are obvious because HPV types 16 and 18 are