

Pharyngeal carriage of *Neisseria meningitidis* and *Neisseria lactamica* in households with infants within areas with high and low incidences of meningococcal disease

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SUMMARY

In a household survey in the Faroe Islands, an isolated community with hyperendemic occurrence of meningococcal disease due to serogroup B 15, 1604 persons were examined for pharyngeal carriage of *Neisseria meningitidis* and *N. lactamica*. Two areas were chosen having experienced high (HIA), and two having experienced low incidences (LIA) of disease. Living in HIA compared with LIA was associated with higher risk of *N. meningitidis* B 15 carriage and lower risk of *N. lactamica* carriage, with odds ratios of 2·7 (95% confidence interval (CI) 1·4-5·1, $P = 0\cdot003$) and 0·41 (95% CI 0·31-0·53, $P < 0\cdot0001$), respectively. In HIA the risk of *N. meningitidis* carriage was much lower in non-carriers than carriers of *N. lactamica*, with an odds ratio of 0·19 (95% CI 0·08-0·47, $P = 0\cdot0003$); in LIA this association (odds ratio 0·51, $P = 0\cdot05$) was much weaker. Children 0-14 years had substantially higher risk of being carriers of *N. meningitidis* group B 15 if the mothers were so, with an odds ratio of 11 (95% CI 4-29, $P < 0\cdot0001$).

INTRODUCTION

As long as an efficient vaccine against serogroup B meningococcal infections is still lacking, it is mandatory to search for other preventive measures against this life-threatening disease. Since symptom-free nasopharyngeal carriage is the usual source of meningococcal disease [1], it is an important element of this strategy to explore further the relationship between nasopharyngeal carriage and disease, as well as to describe factors associated with nasopharyngeal carriage.

The Faroe Islands are a geographically isolated community in the North Atlantic Ocean, between Norway, Iceland and Scotland. During the latter half of the 1970s the incidence of meningococcal disease in the Faroe Islands rose several fold, peaked in 1981 with 95 cases/100 000 (42 cases, population 45000) [2, 3] and by the middle of 1990 [4] it still seems to be higher than in the early 1970s. The

Table 1. Disease incidences during 1981-4, populations, numbers investigated, and response rates in the four areas chosen for study

	Fuglafjörður	Tvöroyri	Western Sandoy	Klaksvík	All four areas
Cases 1981-4	9	12	2*	4	—
Incidence (95% CI)	136 (62; 258)	141 (73; 246)	30 (4; 110)*	21 (6; 53)	—
Population†					
0-4 years	141	139	120	380	590
All ages	1636	2121	1264	4823	9844
Number investigated					
0-4	111	91	102	177	481
All ages	421	310	328	545	1604
Response rates‡					
Among households	79%	65%	85%	93%	82%
Within households	83%	76%	76%	80%	79%

* All villages in Sandoy.

† Populations by 1 January 1985 in the four areas.

‡ Response rate among households: (participating households)/(households asked to participate).

As all mothers of children aged 0-4 years were asked to participate, this was estimated by:

(number investigated of children 0-4 years)/(population of children 0-4 years).

In case of Klaksvík, the denominator was halved, as only half of the mothers were asked to participate (mothers with even birth dates were selected).

Response rate within households: (participating persons)/(all reported members of participating households).

majority of cases were due to sulphonamide resistant *Neisseria meningitidis* group B 15 P1.16, and children 0–4 years were the most frequently affected with an incidence of 400–450 cases/100 000/year [5].

The aim of the present study was to investigate patterns of *N. meningitidis* and *N. lactamica* carriage in this population hyperendemic for meningococcal disease. Not all areas were equally affected, and four geographically well-defined areas on separate islands were chosen, two of which had experienced high and two low incidences of meningococcal disease during the 4 years prior to the investigation (Table 1). The primary study group were children aged 0–4 years, but the corresponding household members were also included. In this report we relate carrier prevalences to disease incidences in the four areas, and to factors like gender and age, carrier status of the mother, and certain environmental factors.

POPULATIONS AND METHODS

Populations and data collection

The Faroese society is a modern one with a highly developed infrastructure. Thus, although the population of about 47000 is distributed on 17 different islands, even the most remote villages are connected by public transport at least once a day with the central areas. During 1981–4 a variation in disease incidence was nevertheless seen between different areas of the islands which could not be attributed to random variation ($P = 0.001$), ranging from 21–141 cases/100 000/year. In order to be able to test for a relationship between disease incidence and prevalence of non-symptomatic carriage at a geographical level, Fuglafjørður and Tvøroyri were chosen to represent areas with high incidences while Western Sandoy and Klaksvík were chosen to represent areas with low incidences (Table 1, Fig. 1). The four areas are located on different islands. Each area covers one village, except Western Sandoy that covers two villages, Skopun and Sandur (originally we planned to include all villages of Sandoy, but due to heavy snow the day of the investigation we only managed to include the two largest villages).

Eligible to the study were households with 0–4 years old children. Rolls of all mothers of such children in the four areas were obtained from the computerized Central Personal Register. In the largest area, Klaksvík, only half of the households were included (mothers that had birth dates with even numbers). Information was given in a letter about the objectives of the study and all members of the household were asked to participate. Furthermore, the mother was asked to fill out an enclosed questionnaire. The families were also encouraged to participate by articles in the newspapers and by announcements over the radio on the day of the investigation; the investigations were undertaken on Saturdays when schools and most working places are closed. On the basis of the questionnaire, supplemented with information obtained when the person was examined, the following data were registered: number of persons belonging to the household, the size of the house, age and sex, whether the mother had work outside the home, and, for preschoolers, whether they attended kindergartens. The investigations took place in the village-schools and were undertaken during the period 2 March to 20 April 1985.



Fig. 1. Map of the Faroe Islands, showing the locations of the four areas selected for the study. K, Klaksvík; WS, Western Sandoy; T, Tvøroyri; F, Fuglafjørður.

Microbiological methods

Swab specimens were taken from both pharyngeal pouches and the swabs were immediately put in Stuart's medium. All investigations were undertaken on Saturdays, therefore all samples were kept in the refrigerator until Monday morning when they were sent by airmail to the Neisseria Department, Statens Seruminstitut, Denmark. On arrival the same evening all specimens were immediately inoculated on Danish GC chocolate agar medium made selective for pathogenic neisseria. Handling of specimens and all laboratory procedures were performed by the same senior technician. Microbiological characterization of the strains will be published separately.

Although we did not assess the actual sensitivity in detecting meningococcal carriage of our swabbing and transportation procedure, we estimate it to be about 80–90% from our earlier experiences (unpublished). As our procedure was standardized this error is likely to be randomly distributed.

Statistical methods

Odds ratios were used to describe associations within 2×2 tables, as this measure of association is easily confounder-adjusted using the method described by Mantel and Haenszel [6]. Confidence intervals of odds ratios were calculated using the test based limits described by Miettinen [7]. Where the word significant is used, it refers to a P -value below 0.05. Despite the close association between the carrier status of mother and child, demonstrated in Table 3, other statistical analyses were done as if the statistical units were individuals rather than households as the interdependence between household members is thought to have negligible effects on the conclusions obtained from those analyses.

RESULTS

Response rates

Eighty-two percent of all the households asked to participate did so, and 79% of all the members belonging to these households participated (Table 1). The comparatively low response rate among households in Tvøroyri (65%) can most certainly be explained by the fact that an unknown number of households in this area received the letter asking them to participate after the actual investigation had taken place. The delay was due to postal irregularities and there seems to be no reason to believe that this has introduced any selection bias. The response rates within participating households were very similar in the four areas.

Area

The overall prevalence of *N. meningitidis* was 26.6% (112/421) in Fuglafjørður, 12.6% (39/310) in Tvøroyri, 9.5% (31/328) in Western Sandoy, and 9.2% (50/545) in Klaksvík; the four prevalences were significantly different ($P < 0.0001$). The overall prevalence of *N. meningitidis* group B 15 was 5.2% (22/421) in Fuglafjørður, 2.7% (8/310) in Tvøroyri, 2.1% (7/328) in Western Sandoy, and 1.1% (6/545) in Klaksvík ($P = 0.001$). The ranking of the overall prevalences of *N. lactamica* was just opposite to that of *N. meningitidis*: 11.4% (48/421) in Fuglafjørður, 18.4% (57/310) in Tvøroyri, 29.9% (98/328) in Western Sandoy, and 28.1% (153/545) in Klaksvík ($P < 0.0001$).

Generally the same rankings were seen within age-strata, with Fuglafjørður highest, Tvøroyri in the middle and Western Sandoy and Klaksvík lowest for *N. meningitidis* carriage; and the opposite for *N. lactamica* carriage.

Disease incidences versus carrier prevalences in the four areas

As illustrated in Fig. 2, disease incidences and carrier prevalences tended to be positively associated for *N. meningitidis* carriage and negatively for *N. lactamica* carriage, although Tvøroyri in *N. meningitidis* carriage tended to be closer in carrier prevalence to the two low incidence areas (Klaksvík and Western Sandoy) than to the other high incidence area (Fuglafjørður).

When pooling the two high incidence areas and the two low incidence areas, the odds ratio of being a carrier of *N. meningitidis* if living in a high incidence area was 2.5 (95% CI 1.9–3.3; $P < 0.0001$), and the odds ratio of being a carrier of *N. meningitidis* group B 15 if living in a high incidence area was 2.7 (95% CI 1.4–5.1, $P = 0.003$). On the other hand, the odds ratio of being a carrier of *N. lactamica* if living in a high incidence area was 0.41 (95% CI 0.31–0.53; $P < 0.0001$). Controlling for age did not change this picture (the odds ratios given here are age-adjusted).

Age and sex

The overall prevalence of *N. meningitidis* carriage was significantly higher in males than in females, 17.2% (122/708) and 11.9% (105/885) respectively, and the corresponding odds ratio of being carrier in males as compared to females was 1.5 (95% CI 1.2–2.0, $P = 0.002$). As can be seen from Fig. 3a, the prevalence of

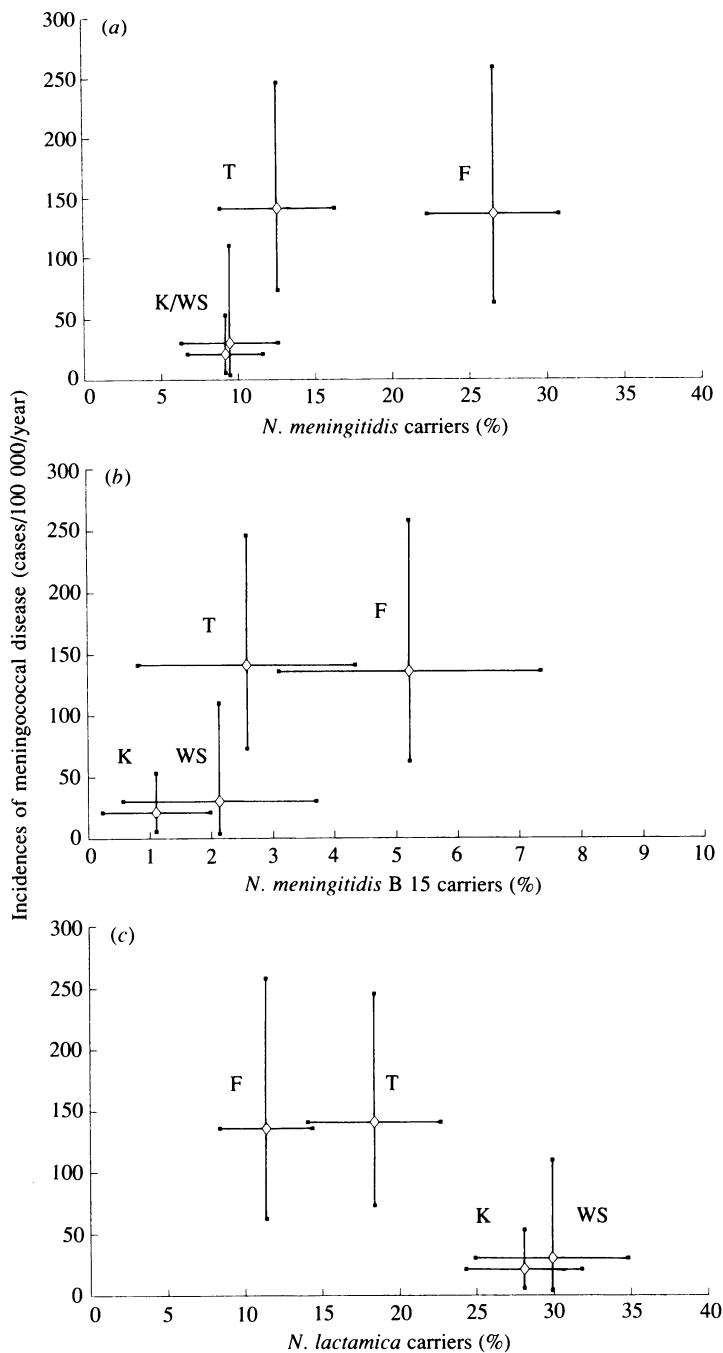


Fig. 2. The relationship between disease incidence (cases/100 000/year) during 1981–4 and the prevalence in the four areas of (a) *Neisseria meningitidis* carriers; (b) *Neisseria meningitidis* B 15 carriers; and (c) *Neisseria lactamica* carriers. The statistical precision of the incidence and the prevalence estimates is indicated by bars representing 95% confidence intervals. K, Klaksvík; WS, Western Sandoy; T, Tvøroyri; F, Fuglafjørður.

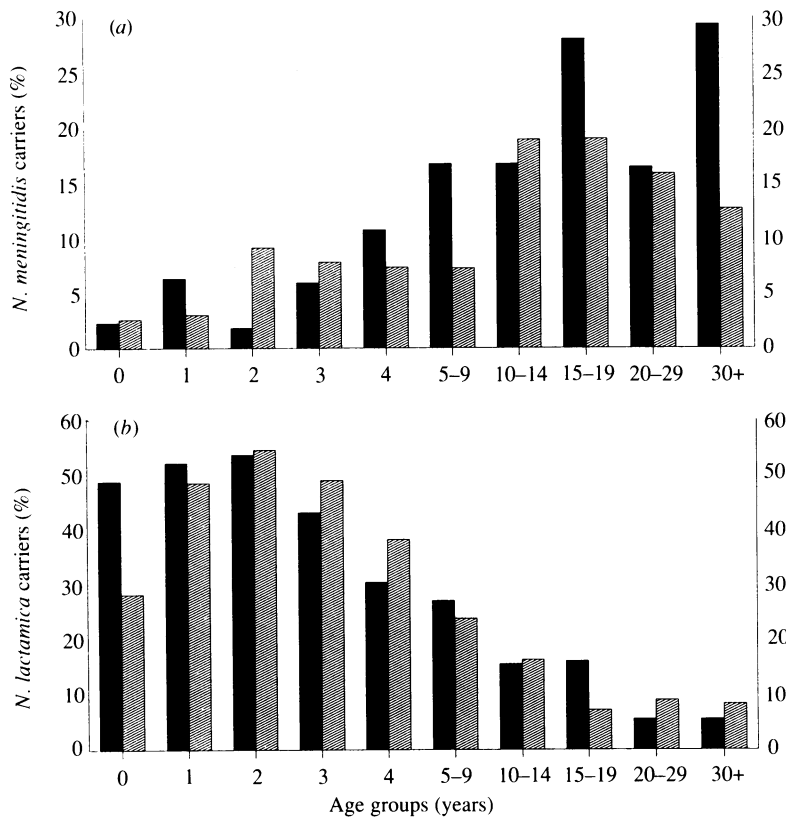


Fig. 3. (a) Prevalence of *Neisseria meningitidis* carriage according to age and sex. (b) Prevalence of *Neisseria lactamica* carriage according to age and sex. Notice that the higher age groups are aggregated. ■, Males; ▨, females.

N. meningitidis carriage increased with age in both sexes (the numbers included in the study of 0, 1, 2, 3, 4, 5-9, 10-14, 15-19, 20-29 and 30+ years old persons were: 43, 48, 56, 51, 56, 126, 84, 25, 55 and 164 males, and 39, 33, 44, 51, 55, 125, 74, 42, 215 and 207 females). Adjusting for confounding by age resulted in a male to female-odds ratio of 1.7 (95% CI 1.3-2.3, $P = 0.0002$). However, a prerequisite of this procedure is that the odds ratio should be independent of age. The test for heterogeneity across age-strata was borderline-significant ($P = 0.06$), and the increased risk of being carrier among males compared to females tended to be most conspicuous in the 5-9, 15-19 and the 30+ years age-groups (Fig. 3a).

The overall prevalence of *N. lactamica* carriage was significantly higher in males than in females, 25.8% (183/708) and 20.0% (177/885) respectively, with a male to female odds ratio of 1.3 (95% CI 1.1-1.7, $P = 0.01$), but adjusting for age reduced the odds ratio to unity, 1.0 (95% CI 0.94-1.1, $P = 0.9$) (test for heterogeneity across age-strata was not significant ($P = 0.3$)). The prevalence of *N. lactamica* carriage decreased steeply with age (Fig. 3b). However, the prevalence tended to peak in the interval from 7 months (not shown in the Figure) to 3 years; thus, in this age group the prevalence was 44.6% (207/447) whereas in the first half year of life the prevalence was 17.2% (5/29) ($P = 0.002$).

Table 2. *The relationship between carriage of Neisseria meningitidis and Neisseria lactamica*

Carrier status*	Fuglafjörður		Tvøroyri		Western Sandoy		Klaksvík		All areas	
	<i>n</i>	%M+	<i>n</i>	%M+	<i>n</i>	%M+	<i>n</i>	%M+	<i>n</i>	%M+
L+, M+	3	6.3	1	1.8	5	5.1	7	4.6	16	4.5
L+, M-	45		56		93		146		340	
L-, M+	109	29.2	38	15.0	26	11.3	43	11.0	216	17.3
L-, M-	264		215		204		349		1032	
Total	421		310		228		545		1604	
Crude odds ratios†		0.16 (0.05; 0.55)		0.10 (0.02; 0.53)		0.42 (0.16; 1.11)		0.39 (0.17; 0.86)		0.22 (0.14; 0.36)
		<i>P</i> = 0.007		<i>P</i> = 0.007		<i>P</i> = 0.08		<i>P</i> = 0.02		<i>P</i> < 0.0001
Age-adjusted odds ratios†		0.20 (0.07; 0.59)		0.17 (0.03; 0.91)		1.19 (0.38; 3.69)		0.48 (0.20; 1.15)		0.28 (0.17; 0.47)
		<i>P</i> = 0.004		<i>P</i> = 0.04		<i>P</i> = 0.8		<i>P</i> = 0.1		<i>P</i> < 0.0001

* L+, M+, carrier of both *Neisseria lactamica* and *Neisseria meningitidis*; L+, M-, carrier of *Neisseria lactamica* but not of *Neisseria meningitidis*; L-, M+, not carrier of *Neisseria lactamica* but of *Neisseria meningitidis*; L-, M-, neither carrier of *Neisseria lactamica* nor of *Neisseria meningitidis*.

† Odds ratio of being carrier of *Neisseria meningitidis* if being carrier of *Neisseria lactamica*. 95% confidence intervals and *P* values are shown.

The age-adjusted odds ratios of being carrier in males versus females were similar in the four areas for both *N. meningitidis* and *N. lactamica*.

N. meningitidis carriage versus N. lactamica carriage

The overall prevalence of *N. meningitidis* carriage among carriers of *N. lactamica* was 4.5%, whereas it was 17.3% among non-carriers of *N. lactamica* (Table 2). The corresponding age-adjusted odds ratio of being a carrier of *N. meningitidis*, if also a carrier of *N. lactamica*, was 0.28 (95% CI 0.17–0.47). However, high and low incidence areas showed different patterns. Thus, the age-adjusted odds ratio did not differ significantly from unity (odds ratio = 1) in the two low incidence areas, Western Sandoy and Klaksvik, whereas it was significantly below unity in the two high incidence areas, where the point estimates were 0.20 and 0.17. In the combined high incidence areas, the age-adjusted odds ratio of being carrier of *N. meningitidis* if also carrier of *N. lactamica*, was 0.19 (95% CI 0.08–0.47, $P = 0.0003$), whereas in the combined low incidence areas it was 0.51 (95% CI 0.26–1.0, $P = 0.05$).

The prevalence of *N. meningitidis* carriage among carriers of *N. lactamica* was quite similar ($P = 0.7$) in the four areas, ranging from 1.8–6.3% (Table 2). On the contrary, the prevalence of *N. meningitidis* carriage among non-carriers of *N. lactamica* differed significantly ($P < 0.0001$) and tended to be highest in high incidence areas (29.2 and 15.0% vs. 11.3 and 11.0%).

Carrier status of mother versus carrier status of child

The prevalence of carriers of *N. meningitidis* among 0–14 years old children having mothers who were themselves carriers was 25.0%, whereas it was 8.8% among those children whose mothers were non-carriers of *N. meningitidis* (Table 3, comparison 1). Since children as well as mothers belonging to high incidence areas are likely to have higher carrier prevalences than others, area is potentially a confounding factor. The area-adjusted odds ratio of the child being a *N. meningitidis* carrier, if the mother was a *N. meningitidis* carrier, was 2.8 (the test for heterogeneity of the odds ratio across area-strata was not significant ($P = 0.6$)). The group of children aged 0–4 years did not have an odds ratio different from that of children aged 5–14 years ($P = 0.3$).

When the type of *N. meningitidis* was considered, the association between the carrier status of the mother and child became even stronger (Table 3, comparisons 2 and 3). Thus, the area-adjusted odds ratio of the child being a carrier of *N. meningitidis* B 15, if the mother was carrier of *N. meningitidis* B 15, was 10.7. Among those 31 mother and child pairs where both were carriers of any type of *N. meningitidis*, the area-adjusted odds ratio of the child being a carrier of *N. meningitidis* B 15, if the mother was carrier of that particular strain, was 38.0.

Effects of house-size, kindergarten, and mother's work

No association could be detected between carriage of *N. meningitidis* and the size of the family house, even after controlling for age, the number of household members, and for the area in which they lived. Children aged 0–4 years attending kindergartens did not have different prevalences of *N. meningitidis* or of

Table 3. *The relationship between carrier status of mother and child (0-14 years). In comparison 1 carrier is defined as being carrier of any Neisseria meningitidis; in comparisons 2 and 3 carrier is defined as being carrier of Neisseria meningitidis, B 15; comparison 3 comprises only those cases where both the mother and the child are carriers of any Neisseria meningitidis*

Combinations of mother-child pairs*	Comparison 1		Comparison 2		Comparison 3	
	<i>n</i>	% Ch +	<i>n</i>	% Ch +	<i>n</i>	% Ch +
Mo +, Ch +	31	25.0	4	17.4	4	80.0
Mo +, Ch -	93		19		1	
Mo -, Ch +	68	8.8	16	1.8	2	7.7
Mo -, Ch -	702		855		24	
Total	894		894		31	
Crude odds ratio†		3.4 (2.2; 5.4) <i>P</i> < 0.0001		11.3 (4.3; 29.2) <i>P</i> < 0.0001		48.0 (6.1; 375.8) <i>P</i> = 0.0002
Area-adjusted odds ratio†		2.8 (1.7; 4.6) <i>P</i> < 0.0001		10.7 (4.0; 28.6) <i>P</i> < 0.0001		38.0 (4.4; 330.5) <i>P</i> = 0.001

* Mo +, Chi +, mother and child both carriers; Mo +, Chi -, mother carrier, but child not carrier; Mo -, Chi +, mother not carrier, but child carrier; Mo -, Chi -, neither mother nor child carrier.

† Odds ratio of child being a carrier if the mother is carrier. 95% confidence intervals and *P* values are shown.

N. lactamica carriage from those of other children, and neither did children whose mothers had work outside the home.

Sulfonamide resistance and N. meningitidis group B 15

There was a strong association between resistance to sulfonamide (MIC \geq 32.0 μ g/ml) and group B 15 strains. Thus, 43/54 (80%) of the group B 15 strains isolated were resistant and 43/63 (68%) of resistant strains were group B 15. Further details on the microbiological characterization will be presented elsewhere.

DISCUSSION

The odds of being carrier of the pathogenic strain of *N. meningitidis*, serogroup B 15, was 2.7 (95% CI 1.4–5.1) times higher in the aggregated high incidence areas than in the aggregated low incidence areas. This finding agrees with the idea that non-symptomatic carriers play a role in disease transmission [1]. It is however noteworthy that in the high incidence areas a general increase was seen in the prevalence of *N. meningitidis* strains, and not only in the prevalence of the serogroup B 15. Thus, the odds of being a carrier of any strain of *N. meningitidis* was 2.5 (95% CI 1.9–3.3) times greater in the high than the low incidence areas.

In the Stonehouse Survey, a rather sharp peak was seen in the age curve for carriage of *N. meningitidis* in the 15–19 years age group [8]. In our study there was a weak tendency for peaking of *N. meningitidis* carriage in the same age-group for females, whereas in males the curve continued to increase up to the age of 40 years after which it tended to plateau. This observation needs to be interpreted with caution because teenagers were not well represented in our study and because males 15 years or older were somewhat under-represented compared to females; this relates to the fact that our study was based on households with 0–4 years old children. The peaking of the prevalence of *N. lactamica* carriage in the age of 7 months to 3 years has also been described in another study [9]. There seems to be controversy about how the carrier prevalence relates to sex. In the Stonehouse survey higher prevalences of *N. meningitidis* carriage were found among males than among females [8], whereas others have found no difference in *N. meningitidis* carriage between the sexes [9–11]. In our study the odds of being a carrier in males compared to females was 1.7 (95% CI 1.3–2.3), but the increased risk in males was primarily seen in the 5–9, 15–19 and the 30+ years age groups.

In a recent report smoking was shown to be an important determinant of meningococcal carriage [12]. Unfortunately no data were collected in our study on smoking habits, but it seems very unlikely that the differences seen between areas in carrier prevalences are confounded by this factor as it is our impression that smoking habits are similar in different areas in the Faroes. Differences in smoking patterns on the other hand, may well account not only for some of the age and sex differences in carrier prevalences in a given population but also for the discrepancies noticed between various populations [8–11] in carrier distributions as to age and sex.

Colonization of the nasopharynx by *N. lactamica* is associated with formation of bactericidal antibodies against meningococci [9], and a high degree of cross-reactivity with antimeningococcal sera has been demonstrated between *N.*

lactamica and *N. meningitidis* strains [13]. The negative association seen in our study between *N. lactamica* carriage and incidence of meningococcal disease, and the negative association between *N. lactamica* carriage and *N. meningitidis* carriage seen in the high incidence areas, provides further support to the view that *N. lactamica* protects against meningococcal infection and pharyngeal colonization. The finding among non-carriers of *N. lactamica*, however, of differing *N. meningitidis* carrier prevalences in high and low incidence areas indicates that other factors than *N. lactamica* carriage also determine the geographical differences in *N. meningitidis* carrier prevalences.

In studies of children with meningococcal disease, associations have been described between carrier status of mother and child [14]. Our survey permitted a study of this relationship in healthy children. The carrier status of mother and child was strongly associated, with an odds ratio of 11 (95% CI 4–29) between mother and child in carriage of *N. meningitidis* B 15. The association could either reflect common environmental or genetic factors predisposing to pharyngeal carriage, or it could reflect bacterial transmission between mother and child, possibly both. In spite of this strong association, however, it should be noted that in only 4 of the 20 children who were carriers of *N. meningitidis* B 15, were their mothers also carriers of this strain (Table 3). Thus only a limited proportion of the overall occurrence of *N. meningitidis* B 15 carriage among children could be related to maternal carriage of this strain, with a 'population attributable fraction' of 18% $(20/894 - 16/871)/(20/894)$ (population attributable fraction [15] is the proportion of the diseased, here carriers among children, that is attributable to a certain factor of interest, here having a mother that is also carrier; the term implies that the observed statistical association reflects causality which need not be the case). Unfortunately, it was not possible to make a similar analysis for other family members, like the father.

The failure to find an association between the prevalence of being a carrier of *N. meningitidis* on the one hand and the size of the house and whether the child attended kindergarten on the other, are compatible with the findings of others [10]. We did not find an increased risk of meningococcal carriage among babies whose mothers worked outside the home, and we found no study evaluating this relationship.

One general weakness of the cross-sectional design used here, is that it fails to separate the associated parameters temporally. Assuming that the associations observed reflect causal relationships, it is impossible to point out which of the associated factors are the primary ones in the causal chains. Longitudinally designed studies are therefore needed to document the suggested protective role of *N. lactamica* carriage and the significance of the carrier status of the parents, for the child's risk of contracting meningococcal colonization and infection.

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