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# The response to inactivated influenza A (H3N2) vaccines: the development and effect of antibodies to the surface antigens

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SUMMARY

A controlled trial of influenza vaccines in a boys' public school from November 1970 to October 1975 provided an opportunity to study the response to vaccine and the effect on subsequent natural challenge in boys with differing natural experience of influenza A strains. The response to influenza A (H3N2) vaccines was assessed by estimating homotypic and heterotypic antibodies to the surface antigens. Previous natural experience of influenza A was found to influence vaccine response and the effect of natural challenge. The antibody response to revaccination with the same strain showed a progressively poorer response to second and third doses. The protective effect of naturally acquired and vaccine-induced antibodies was assessed during two outbreaks of influenza A which occurred in the trial period.

## INTRODUCTION

Tyrrell (1976) has pointed out that the only final test of the potency of a vaccine is its ability to protect against disease following exposure in an epidemic. To obtain a valid assessment of vaccine effectiveness in a field trial substantial organization is required. Vaccine and matched control groups of adequate size have to be recruited, vaccinated and monitored. The trial population must then have the good fortune to experience an epidemic at an appropriate time with a high enough attack rate to enable significant differences between groups to be observed. Laboratory confirmation of all clinical cases is essential. Evidence of infection in atypical cases and an assessment of infection rates in those with no symptoms is desirable if the whole effect of the vaccine is to be estimated.

A search of the literature suggests that these circumstances are rarely encountered. Much work has been done on the serological responses to vaccines of different types (Pereira *et al.* 1972; Mostow *et al.* 1973; Smith *et al.* 1975). The response to challenge with live virus has been studied in animals (Kaye, Dowdle & McQueen, 1969; McLaren, Potter & Jennings, 1974) and more recently in human volunteers (Potter *et al.* 1975; André *et al.* 1976). Another approach has been to use large study populations and to compare recorded illness in vaccinated and control groups. Low vaccine acceptance rates and low attack rates during local or national epidemics have made assessment of protection inconclusive (Smith, Fletcher & Wherry, 1976). MacKenzie, MacKenzie, Lloyd & Dent (1975) concluded that retrospective self-diagnosis provides little useful information on influenza attack rates.

Previous reports (Hoskins *et al.* 1973, 1976) have described a trial of inactivated influenza vaccines in a boys' boarding school. During two outbreaks of influenza A it was shown that boys who received a vaccine containing an immediate precursor to the epidemic strain had a lower attack rate than boys not so vaccinated. The circumstances of the trial made it possible to compare the protective effect of vaccination with that of natural infection and to study the antibody responses. The response to natural infection with influenza A in boys who had received only influenza B vaccine has been reported (Smith & Davies, 1976). The results presented here show the response to vaccine and the effect of natural challenge in boys who received inactivated influenza A vaccine.

## MATERIALS AND METHODS

The trial started in October 1970 when boys whose parents had consented were allocated by date of birth to receive either influenza A or B vaccine. Each year new entrants joined the trial and boys already in the school were revaccinated. Blood samples were obtained on entry to the trial and at various times thereafter. Details of the vaccines used and assessments made are shown in Table 1. The vaccines were supplied by Evans Medical Ltd., Speke.

All boys who reported to the school medical officer with an influenza-like illness were investigated. Throat swabs were examined for pathogenic bacteria and viruses and paired sera were collected.

Sera were examined for antibodies to the haemagglutinin and the neuraminidase using the techniques previously described (Smith & Davies, 1976). The viruses used were as follows:-

*For haemagglutinin antibody estimations (HI)*

H2N2 strain:

| | |
|---|---|
| A/England/12/64 | A/Eng/64 |

H3N2 strains:

| | |
|---|---|
| A/Hong Kong/1/68 | A/HK/68 (HK) |
| A/England/42/72 | A/Eng/72 (72) |
| A/Port Chalmers/1/73 | A/PC/73 (PC) |

were obtained from Dr M. S. Pereira, Virus Reference Laboratory, Colindale, England.

| | |
|---|---|
| A/Scotland/840/74 | A/Scot/74 |

was obtained from Dr G. C. Schild, W.H.O. World Influenza Centre, London.

*For neuraminidase antibody estimations (N)*

| | |
|---|---|
| A/equine/Prague/1/56 (Heq 1) × A/Hong Kong/1/68(N2) | × 15 |
| A/equine/Prague/1/56 (Heq 1) × A/England/42 72(N2) | × 38 |
| A/equine/Prague/1/56 (Heq 1) × A/Port Chalmers/1/73(N2) | × 42 |

were obtained from Dr G. C. Schild.

Table 1. *Vaccination and blood sampling schedules*

| Year of entry | No. of boys | 1970 Nov. | 1971 Oct. | 1972 Oct. | 1973 Nov. | 1974 Mar. | 1974 May | 1974 Oct. | 1975 Oct. | Assessment: |
|---|---|---|---|---|---|---|---|---|---|---|
| 1970 | 71 | A/HK/Vac* B.S.† | A/HK/Vac B.S. | A/HK/Vac B.S. | . B.S. | . | B.S. (59 boys) | . | . | Vaccine response to 1st, 2nd and 3rd doses of A/HK/Vac. Infection in 1972 and 1974 |
| 1972 and 1973 | 78 | . | . | . | A/Eng/Vac B.S. | B.S. | . | . | . | Vaccine response to A/Eng/Vac |
| 1972 | 26 | . | . | A/HK/Vac | A/Eng/Vac B.S. | B.S. | . | . | . | Vaccine response to A/Eng/Vac following A/HK Vac |
| 1974 | 95 | . | . | . | . | . | . | A/PC/Vac B.S. | A/PC/Vac B.S. | Vaccine response to A/PC/Vac |

* A/HK/Vac = A/Hong Kong/X31/68, (200 i.u.).
A/Eng/Vac = A/England/42/72 (XPR8) (180–200 i.u.).
A/PC/Vac = A/England/42/72(XPR8) (100 i.u.).
+A/Port Chalmers/1/73(XPR8) (300 i.u.).

† B.S. = blood sample collected.

It has been suggested (Slepushkin *et al.* 1971; Miller *et al.* 1973) that apparent low titre HI antibody to A/HK/68 may result from infection with Asian (H2N2) strains due to the common neuraminidase. Sera from boys showing evidence of infection with Asian strains (i.e. with HI antibodies to A/Eng/64 and N antibodies to $\times 15$) who also had HI antibody to A/HK/68 but not to later members of the H3N2 subtype were titrated against a recombinant virus A/Hong Kong/1/68 (H3) $\times$ A/equine/Prague/1/56 (Neq 1) obtained from Dr G. C. Schild. Only those with HI antibody to the recombinant (H3 Neq 1) were regarded as showing evidence of infection with H3N2 strains.

In the tables that follow those sera with an HI antibody tire of 1/20 or more are recorded as 'with antibody' and those with a titre of less than 1/20 as 'without antibody'. In neuraminidase antibody tests a titre of 1/10 or more is recorded as 'with antibody'.

## RESULTS

### *Response to vaccine*

Assessment of vaccine response was generally made a year after vaccination when the boys were bled before being revaccinated (Table 1). It seemed possible that this might result in a considerable under-estimate of the vaccine response. An opportunity to assess the significance of this under-estimate occurred on two occasions. In March 1971 there was a small outbreak of influenza B in the school and 21 boys of the 1970 entry were bled; in March 1974 there was another outbreak of influenza B and 19 boys of the 1973 entry were bled. A comparison of the antibody titres in these 40 sera, collected 4 months after vaccination, with the subsequent annual sera showed the extent to which any fall in antibody over this period might distort estimates of response.

In 27 of the 40 boys the HI antibody titres were the same in March and October and a further 10 boys, though showing a fall in titre, would still have been classified as responders. In three boys a homotypic response was maintained but cross-reacting heterotypic antibodies were lost. Estimates of response to the neuraminidase antigens showed a similar pattern; 33 boys had the same titres in March and October, one showed a fall in titre but would still have been classified as a responder and three boys maintained a homotypic response but heterotypic antibodies were lost. Three boys had an apparent twofold rise in homotypic antibody in the March sera but the annual sera collected before and after vaccination gave the same titres.

It seems, therefore, that antibodies produced after vaccination are sufficiently well maintained to make the results of the annual sera a reasonable estimate of vaccine response. This impression is supported by the small changes in the geometric mean titres (GMT) between the March and October sera which for no antigen exceeded a 25% fall. Smith *et al.* (1975) showed that antibodies produced following aqueous influenza A vaccine are still detectable over a year after vaccination.

Table 2. *Homotypic antibody response to first dose of vaccine*

| Pre-existing HI antibody | Response after first dose of: A/HK/Vac (71 boys) | | | | A/Eng/Vac (78 boys) | | | | A/PC/Vac (95 boys) | | | | Total | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HI+N* | HI | N | NR | HI+N | HI | N | NR | HI+N | HI | N | NR | HI+N | HI | N | NR |
| No H3 | 25 | 15 | 0 | | 5 | 4 | 0 | 3 | | None | | | 30 | 19 | 0 | 7 |
| | | | | | | | | | | | | | | 56 | | |
| H3 but not homotypic | | None | | | 3 | 12 | 0 | 1 | 3 | 6 | 2 | 0 | 6 | 18 | 2 | 1 |
| | | | | | | | | | | | | | | 27 | | |
| Homotypic | 2 | 16 | 1 | 8 | 8 | 24 | 0 | 18 | 11 | 39 | 2 | 32 | 21 | 79 | 3 | 58 |
| | | | | | | | | | | | | | | 161 | | |
| Total (%) | 27 (38) | 31 (44) | 1 (1) | 12 (17) | 16 (21) | 40 (51) | 0 — | 22 (28) | 14 (15) | 45 (47) | 4 (4) | 32 (34) | | | | |

* HI+N = response to haemagglutinin and neuraminidase.
HI = response to haemagglutinin only.
N = response to neuraminidase only.
NR = no response.

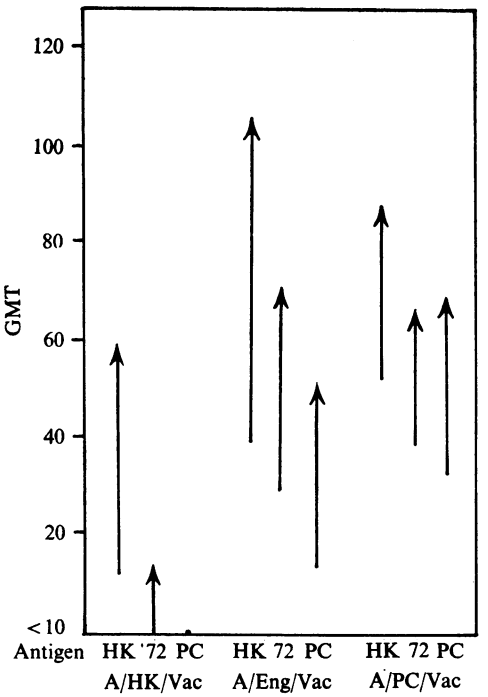


Fig. 1. Response by HI titre to first dose of vaccine.

*Response to first dose of vaccine*

The serological response to vaccine can be considered in two ways; the homotypic response to the vaccine strain and the production of antibodies which cross-react with future antigenic variants – the heterotypic response.

The homotypic response to the first dose of the three vaccines is shown in Table 2 where the results are related to prevaccination antibody state. The heterotypic response to the haemagglutinin is shown in Fig. 1 where the rise in GMT of antibody to the three antigens is plotted. Table 3 shows the antibody state of each vaccine group before and after vaccination.

It is clear that the three groups differed considerably in their past experience of the H3N2 subtypes. Many of the 1970 entry had no evidence of natural infection with A/Hong Kong strains. The 1973 entry had had much more natural experience of H3N2 stranis and it seems likely that about a quarter of them had been infected with A/Eng/72. (The reasons for this assumption are given later.) The 1974 entry had all had some experience of H3N2 strains, much of it probably by natural infection with strains similar to A/Eng/72 or A/Port Chalmers/73.

It is apparent from Table 2 that past natural experience influenced the response to vaccine. Those encountering the H3 antigen for the first time generally responded well, over half produced antibodies to both the haemagglutinin and neuraminidase antigens, a few failed to respond. Those with some experience of the H3 antigen but no homotypic HI antibodies to the vaccine strain generally produced a response to the haemagglutinin only. Those with homotypic antibody responded least well – about a third failing to respond at all.

Table 3 *Antibody state before and after first dose of vaccine*

| Antibody state:* | | | | | | A/HK/Vac (71 boys) | | A/Eng/Vac (78 boys) | | A/PC/Vac (95 boys) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HI | | | N | | | | | | | | |
| HK | 72 | PC | X15 | X38 | X42 | Before | After | Before | After | Before | After |
| − | − | − | + | − | − | 44 | 4 | 12 | 3 | 0 | 0 |
| + | − | − | + | − | − | 6 | 24 | 5 | 1 | 0 | 0 |
| + | − | − | + | + | − | 8 | 11 | 10 | 0 | 0 | 0 |
| + | − | − | + | + | + | 0 | 1 | 1 | 0 | 0 | 0 |
| + | + | − | + | − | − | 5 | 8 | 3 | 1 | 5 | 0 |
| + | + | − | + | + | − | 5 | 6 | 10 | 0 | 5 | 0 |
| + | + | − | + | + | + | 0 | 0 | 1 | 0 | 1 | 2 |
| + | + | + | + | − | − | 2 | 8 (1)† | 2 (2) | 10 (10) | 9 (1) | 6 |
| + | + | + | + | + | − | 1 | 9 (4) | 13 (5) | 34 (26) | 39 (14) | 37 (29) |
| + | + | + | + | + | + | 0 | 0 | 21 (14) | 29 (26) | 36 (31) | 50 (48) |

* +, Antibody present; −, antibody not detected. (Antigens described in text.)
† Figures in parentheses indicate boys with HI antibody to A/Scot/74.

The heterotypic response was also determined by previous natural experience. Considering only those who had a response to A/HK/Vac, 17 of the 40 boys who had no H3 antibody in their pre-vaccination sera produced heterotypic antibody compared with 17 of the 19 boys with H3 antibody initially. The boys given A/Eng/Vac were better naturally endowed and all but two of those who responded produced heterotypic antibody. Of the boys given A/PC/Vac all but three of those who responded made a heterotypic response as judged by the production of antibody reacting with the A/Scot/74 haemagglutinin.

*Response to revaccination with the same strain*

The response to the second dose of A/HK/Vac was poor. Of the 71 boys assessed 50 failed to respond, 16 responded to the haemagglutinin only, 4 to the neuraminidase only and one boy to both. All but four of those who responded produced heterotypic antibody. However, the antibody titre in those who failed to respond to the second dose of vaccine did not fall during the year.

An assessment of the response to the third dose of A/HK/Vac was complicated by an outbreak of influenza A in the school in December 1972. This outbreak was caused by a strain similar to A/Eng/42/72 and started 6 weeks after vaccination and 10 days before the end of term. A number of boys in both the vaccinated and the control groups reported that they had an influenza-like illness in the first week of the holidays. Confirmation that this illness was influenza was obtained in all of 17 boys in the control group. They showed a significant rise in antibodies between October 1972 and November 1973. As reported previously (Smith & Davies, 1976), an additional 21 boys in the control group who reported no influenza-like symptoms also showed evidence of infection during the year.

The antibody response in the 52 naturally infected boys in the control groups, assessed in November 1973, can be summarized as follows:

HI antibodies – All had antibody reacting with the homotypic strain (A/Eng/72 and with A/PC/73; 40 boys had antibody reacting with A/Scot/74.

Antibodies to the neuraminidase –

Five boys failed to produce homotypic antibody (× 38) and a further two boys did not produce antibody reacting with the A/PC neuraminidase (× 42). All the rest (45) produced both homotypic and heterotypic antibodies.

After the first dose of A/HK/Vac only 5 of the 71 vaccinated boys produced antibody reacting with the A/Scot/74 haemagglutinin and one other produced antibody reacting with the A/PC neuraminidase but none produced antibody reacting with both of these antigens. After the second dose there was no further production of these heterotypic antibodies. It was decided that those boys in the A/HK/Vac group who, during the year 1972–3, produced antibody both to the A/PC neuraminidase and to the A/Scot/74 haemagglutinin must be regarded as having been infected. This included the four confirmed cases which occurred during the term and 14 of the 15 boys who reported an influenza-like illness during the holidays. It also included six boys who had no symptoms of influenza. This probably underestimates the number of infected since, as has already been shown, not all of the boys with confirmed infections produced such a broad heterotypic response. In fact five additional boys might have been regarded as infected had the criteria been made less severe; four, who had no symptoms, developed HI antibodies to A/Scot/74 but no antibody to the A/PC neuraminidase and one, who was ill in the holidays, developed antibodies to the haemagglutinin and neuraminidase of A/PC/73 but no antibody to A/Scot 74. These boys have nevertheless been regarded in this estimate of vaccine response and in the subsequent assessment of the effect of vaccine as making a response to the third dose of A/HK/Vac.

Excluding the 24 boys considered to have been infected with A/Eng/42/72 the response to the third dose of vaccine by the remaining 47 boys was as follows:

| | |
|---|---|
| No response | 37 |
| Response to haemagglutinin only | 8 |
| Response to haemagglutinin and neuraminidase | 2 |

*Response to A/Eng/Vac in boys previously vaccinated with A/HK/Vac*

Twenty-six boys who had received a single dose of A/HK/Vac were revaccinated with A/Eng/Vac (see Table 1). At the time of revaccination all but five had HI antibody to A/Eng/72, either naturally acquired or produced in response to their first dose of vaccine. The response to A/Eng/Vac was similar to that of boys who received this as their first vaccine (see Table 2). Sixteen responded to the haemagglutinin only, two to both haemagglutinin and neuraminidase and eight failed to respond.

*Effect of A/HK/Vac*

There were two opportunities to assess the effect of the A/HK/Vac. One, already referred to, occurred in 1972 during the outbreak of influenza caused by A/Eng/42/72 and the other occurred in 1974 during an outbreak caused by A/Port Chalmers. Fifty-nine vaccinated boys were assessed throughout the period and all had

Table 4. *Fate of 115 boys fully assessed*

| Initial state (1970) | | Total | Infected 1971–72 (Oct.) S* | Infected 1971–72 (Oct.) NS* | Infected 1972 (Dec.) S | Infected 1972 (Dec.) NS | Infected 1974 S | Infected 1974 NS | Not infected |
|---|---|---|---|---|---|---|---|---|---|
| No H3 antibody | No vaccine | 30 | 1 | 5 | 13 | 7 | 3† | 2† | 1 |
| | A/HK/Vac ×3 | 34 | . | . | 12 | 5 | 7 | 6 | 4 |
| With H3 antibody | No vaccine | 26 | 0 | 1 | 8 | 5 | 2 | 4 | 6 |
| | A/HK/Vac ×3 | 25 | . | . | 3 | 0 | 6 | 5 | 11 |

* S, With symptoms of influenza; NS, without symptoms of influenza.
† Includes one boy infected 1971–2.

Table 5. *HI antibody response to three doses of A/HK/Vac in boys infected in two outbreaks*

| Fate | Antigen | Initial state No.* | Initial state GMT | After 1st dose No. | After 1st dose GMT | After 2nd dose No. | After 2nd dose GMT | After 3rd dose No. | After 3rd dose GMT |
|---|---|---|---|---|---|---|---|---|---|
| Infected | HK | 3 | < 10 | 17 | 44 | 18 | 52 | . | . |
| 1972 | 72 | 0 | < 10 | 2 | < 10 | 4 | < 10 | . | . |
| (20 boys) | PC | 0 | < 10 | 0 | < 10 | 1 | < 10 | . | . |
| Infected | HK | 11 | 15 | 24 | 81 | 24 | 84 | 24 | 81 |
| 1974 | 72 | 7 | < 10 | 17 | 22 | 19 | 27 | 20 | 29 |
| (24 boys) | PC | 3 | < 10 | 10 | 14 | 14 | 17 | 12 | 17 |
| Not | HK | 11 | 26 | 15 | 83 | 15 | 79 | 15 | 87 |
| infected | 72 | 3 | < 10 | 10 | 26 | 11 | 24 | 12 | 30 |
| (15 boys) | PC | 1 | < 10 | 5 | 12 | 7 | 14 | 10 | 17 |

GMT = reciprocal geometric mean titre of group.
* Number with antibody.

received three doses of A/HK/Vac, the last dose being given before the 1972 outbreak. They were not revaccinated after this. A group of 56 boys who had received no influenza A vaccine but were similarly assessed acted as controls. The fate of the boys in two outbreaks is shown in Table 4.

No evidence of infection was detected in the control group during the first year (1970–1) and seven boys in this group were infected in the school year ending October 1972. One had clinical influenza and an A/Hong Kong-like strain was isolated. It is not possible to be certain that no infection occurred in the vaccine group over this period since rises in antibody titre attributable to vaccine would not be distinguishable from a response to infection with the influenza strains then in circulation in this country. None had an influenza-like illness and it is unlikely that they were infected (see response to second dose of vaccine.)

It will be seen from Table 4 that the effect of vaccination on infection in 1972 was most marked in those who entered the trial with some natural antibody to H3N2 strains. There is no suggestion that vaccine had any effect in determining the outcome of infection, i.e. whether or not it resulted in symptoms of influenza. None of those infected in 1972 was re-infected in 1974. The infection rate in 1974

Table 6. *Effect of homotypic antibody on infection*

| Year: | | Homotypic antibody before outbreak: None | HI* | N | HI + N |
|---|---|---|---|---|---|
| 1972 | Total – 71 | 22 | 21 | 10 | 18 |
| | Infected | 14 | 2 | 6 | 2 |
| | Not infected | 8 | 19 | 4 | 16 |
| 1974 | Total – 59 | 17 | 21 | 0 | 21 |
| | Infected | 12 | 12 | 0 | 0 |
| | Not infected | 5 | 9 | 0 | 21 |

* See footnote to Table 2.

in those not infected in 1972 was slightly higher in the vaccinated group (24/39) than in the control group (11/23) but this differences is not statistically significant ($P \simeq 0{\cdot}3$).

Considering only those with symptoms, there were 27 cases of influenza in the 56 boys in the control group over the 4 year period and 28 cases in the vaccine group of 59 boys.

An attempt to correlate infection in the two outbreaks with the response to vaccine is given in Table 5. It will be seen that those infected in 1972 were boys with the least natural HI antibody initially, who made the poorest response to vaccine. Those spared in 1972 but infected in 1974 and those not infected in either outbreak were similar both in their initial antibody state and in their response to vaccine. This table also shows the poor response to the second and third doses of A/HK/Vac.

An estimate of the effect of antibody on infection rates in 1972 is complicated by the fact that the boys were bled and then given a third dose of A/HK/Vac 6 weeks before the outbreak started. However, since the response to the third dose was so poor and only three of those who responded developed antibody to the A/Eng/72 antigens, the antibody state at the time of vaccination gives some indication of the probable state at the time of the outbreak. The antibody state of boys assessed in the 1974 outbreaks is taken to be that of the blood collected 4 months earlier.

The infection rates in 1972 and 1974 by homotypic antibody state is shown in Table 6. In 1972 infection was related to the presence or absence of homotypic HI antibody irrespective of whether this was natural or vaccine induced. Antibody to the neuraminidase antigen was not correlated with infection. In the 1974 outbreak the infection rate was similar in those who had HI antibody only and those who had no antibody to A/PC/73. Those infected in 1972 and who (by definition – see above) had antibody to both the haemagglutinin and neuraminidase were not infected.

It is unfortunately not possible to assess the effect of A/Eng/Vac. Many of the boys who received this vaccine in November 1973 had antibody to the A/Port Chalmers antigens in their prevaccination sera (see Table 3). Since the outbreak of 1972 had produced some evidence for the protective effect of inactivated influenza A vaccine (Hoskins *et al.* 1973) it was not considered ethical to withold it from new

entrants. There was therefore no comparable control of similar prevaccination experience. Ten cases of influenza A/Port Chalmers occurred in the 210 boys who had received A/Eng/Vac.

## DISCUSSION

The serological response to the first dose of inactivated influenza A vaccine depended upon experience of the same or a related antigen. Those boys with no antibody to the haemagglutinin of A/HK/68 (H3) generally responded by producing antibody to both the haemagglutinin and the neuraminidase of the vaccine strain. The response in those with antibody to the H3 antigen was generally confined to the haemagglutinin. However, those who responded usually produced antibody reacting with future strains. Those who already had antibody to the vaccine strain, whether acquired by natural infection or a previous dose of vaccine, often failed to respond but when they did they produced a heterotypic response. As judged by antibody response there seems little advantage in revaccinating with the same strain.

The results presented here (Table 6) illustrate the problem of trying to predict immunity to infection from an estimate of serum antibodies. In the first outbreak (1972) 4 of the 39 boys with homotypic HI antibody were infected compared with 20 of the 32 boys with none. Neuraminidase antibody apparently made no contribution to protection; 8 of 28 boys with homotypic neuraminidase antibody were infected compared with 16 of 43 boys with none. In this outbreak, therefore, the presence of homotypic HI antibody correlated with protection. However, in the second outbreak those with homotypic HI antibody only were infected to the same extent as those with none, whereas those with homotypic antibody both to the haemagglutinin and the neuraminidase were not infected. This may be explained by a difference in the antigenic stimulus. Before the 1972 outbreak antibodies to the epidemic strain (A/Eng/72) had resulted from infection or vaccination with A/HK-like strains. In 1974 those with antibodies to both the haemagglutinin and neuraminidase of A/Port Chalmers had acquired these from infection with A/Eng/72 whereas those with HI antibodies only had acquired them by natural infection or vaccination with A/HK strains. This would suggest that those with experience of one strain may be relatively or completely immune to a closely related strain but further antigenic drift renders them susceptible even though they have cross-reacting antibodies. It is of interest to compare these findings with those previously reported in boys of the control group whose antibodies resulted entirely from natural infection (Smith & Davies, 1976). In both the 1972 and 1974 outbreaks immunity was equally well predicted by the presence of homotypic antibody to the haemagglutinin or to the neuraminidase. None of those infected in 1972 was re-infected in 1974.

The purpose of vaccination is, of course, to protect against clinical influenza. The extent to which this is achieved will depend upon a number of factors:

the antigenic characteristics of the infecting strain,
the proportion of the population susceptible to it,
the infection rate,
the attack rate in those infected.

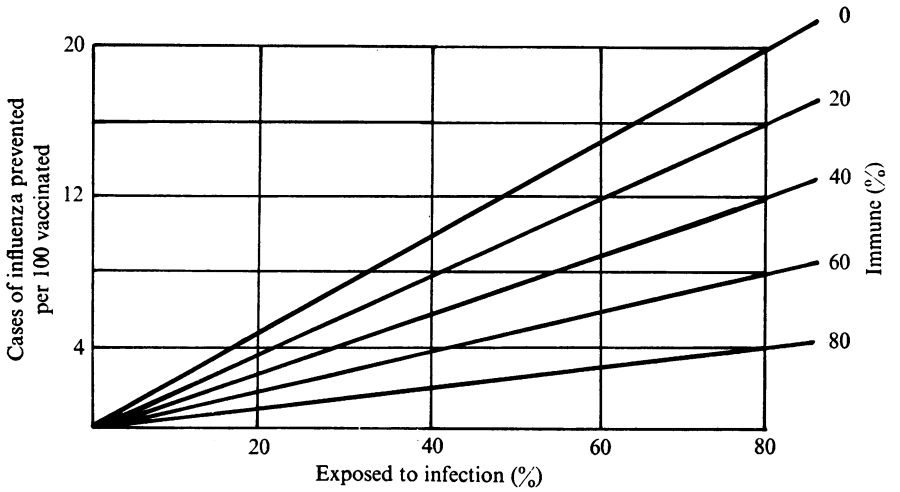


Fig. 2. Effect of influenza vaccination on a community. Assumptions: (1) vaccination will be 50% effective in preventing infection; (2) of those infected 50% will have clinical influenza.

In recent years vaccines available have contained the strains of influenza A characteristic of those circulating in the previous winter. However, the antigenic drift of the virus has resulted in those vaccinated being challenged (if at all) by a strain somewhat different from that in the vaccine.

If certain assumptions are made it is possible to assess the likely overall effectiveness of a vaccine to a community. The first assumption concerns the efficiency of the vaccine in preventing infection. Our own experience and that of Stiver, Graves, Eickhoff & Meiklejohn (1973) suggests that this may be about 50%. The second assumption concerns the proportion of those infected who will develop clinical influenza. This may be characteristic of the strain but, based on the two outbreaks reported here, would seem unlikely to exceed 50%. This estimate is similar to the experience of Miller *et al.* (1973); other workers (Stiver *et al.* 1973; Mair, Sansome & Tillett, 1974) suggest that a much lower proportion of those infected will report symptoms of influenza. In Fig. 2 the effect of the vaccine, as measured by the number of cases of influenza prevented in 100 people vaccinated, is shown for populations of various degrees of immunity and exposed to various degrees of challenge. In the general population where the proportion challenged by natural infection is seldom likely to reach 20% the impact of an outbreak is unlikely to be appreciably modified by vaccination unless the immunity of the population is very low and acceptance of the vaccine very high. In a closed community where spread of the challenge virus may be more efficient a useful protective effect may be achieved. In a boarding school such as the one where this vaccine trial was carried out the effect may be to reduce the size of an outbreak to manageable proportions, although for the individual it may seem that the inevitable has merely been postponed.

We would like to thank Dr Hoskins, the staff of the School Infirmary and the boys of Christ's Hospital, Horsham, for their co-operation; Dr G. C. Schild and Dr M. S. Pereira for supplying the viruses and Dr C. L. Miller and the staff of the Epidemiological Research Laboratory, Colindale, who organized the vaccine trial.

## REFERENCES

André, F. E., Uytterschaut, P., Niculescu, I. T. I., Virlan, G., Zilisteanu, E., Smerdel, S. & Vodopija, I. (1976). Placebo-controlled double-blind clinical studies on the efficacy of different influenza vaccines assessed by experimental and natural infection. *Postgraduate Medical Journal* **52**, 352.

Hoskins, T. W., Davies, J. R., Allchin, A., Miller, C. L. & Pollock, T. M. (1973). Controlled trial of inactivated influenza vaccine containing the A Hong Kong strain during an outbreak of influenza due to the A/England/42/72 strain. *Lancet* ii, 116.

Hoskins, T. W., Davies, J. R., Smith, A. J., Allchin, A., Miller, C. L. & Pollock, T. M. (1976). Influenza at Christ's Hospital, March 1974. *Lancet* i, 105.

Kaye, H. S., Dowdle, W. R. & McQueen, J. L. (1969). Studies on inactivated influenza vaccine. 1. The effect of dosage on antibody response and protection against homotypic and heterotypic challenge in mice. *American Journal of Epidemiology* **90**, 162.

MacKenzie, J. S., MacKenzie, I., Lloyd, J. & Dent, V. (1975). Comparative trials of live attenuated and detergent split influenza virus vaccines. *Journal of Hygiene* **75**, 425.

McLaren, C., Potter, C. W. & Jennings, R. (1974). Immunity to influenza in ferrets. XI. Cross-immunity between A/Hong Kong/68 and A/England/72 viruses: serum antibodies produced by infection and immunization. *Journal of Hygiene* **73**, 389.

Mair, H. J., Sansome, D. A. W. & Tillett, H. E. (1974). A controlled trial of inactivated monovalent influenza A vaccines in general practice. *Journal of Hygiene* **73**, 317.

Miller, D. L., Reid, D., Diamond, J. R., Pereira, M. S. & Chakraverty, P. (1973). Hong Kong influenza in the Royal Air Force 1968–70. *Journal of Hygiene* **71**, 535.

Mostow, S. R., Dowdle, W. R., Schoenbaum, S. C., Coleman, M. T. & Kaye, H. S. (1973). Inactivated vaccines. 1. Volunteer studies with very high doses of influenza vaccine purified by zonal ultra-centrifugation. *Postgraduate Medical Journal* **49**, 152.

Pereira, M. S., Chakraverty, P., Schild, G. C., Coleman, M. T. & Dowdle, W. R. (1972). Prevalence of antibody to current influenza viruses and effect of vaccination on antibody responses. *British Medical Journal*, iv, 701.

Potter, C. W., Jennings, R., McLaren, C. Edey, D. & Stuart-Harris, C. H. (1975). A new surface-antigen-adsorbed influenza virus vaccine. *Journal of Hygiene* **75**, 353.

Slepushkin, A. N., Schild, G. C., Beare, A. S., Chinn, S. & Tyrrell, D. A. J. (1971). Neuraminidase and resistance to vaccination with live influenza A2 Hong Kong vaccines. *Journal of Hygiene* **69**, 571.

Smith, A. J. & Davies, J. R. (1976). Natural infection with influenza A (H3N2). The development, persistence and effect of antibodies to the surface antigens. *Journal of Hygiene* **77**, 271.

Smith, J. W. G., Fletcher, W. B., Peters, M., Westwood, M. & Perkins, F. J. (1975). Response to influenza vaccine in adjuvant 65–4. *Journal of Hygiene* **74**, 251.

Smith, J. W. G., Fletcher, W. B. & Wherry, P. J. (1976). Vaccination in the control of influenza. *Postgraduate Medical Journal* **52**, 399.

Stiver, H. G., Graves, P., Eickhoff, T. C. & Meiklejohn, G. (1973). Efficacy of 'Hong Kong' vaccine in preventing 'England' variant influenza A in 1972. *New England Journal of Medicine* **289**, 1267.

Tyrrell, D. A. J. (1976). Assessment of vaccine efficacy by challenge studies in man. *Postgraduate Medical Journal* **52**, 379.