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The relationship between epidemic influenza A(H_1N_1) and ABO blood groups

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SUMMARY

An outbreak of influenza caused by the A(H_1N_1) subtype in military recruits in February 1978 afforded an opportunity to study the association of ABO blood groups with influenza morbidity and serological response. Fifty-eight per cent of 336 recruits became clinically ill. There was no differential distribution of clinical influenza by blood group. However, seroconversion to a titre of $\geqslant 20$ was significantly and appreciably higher in groups A and B than O and AB. Also, among those with serologically confirmed clinical influenza, the occurrence was significantly higher in groups A and B than groups O and AB.

INTRODUCTION

Several studies of the association of ABO blood groups with clinical and serological influenza during the past decade have produced inconsistent results (McDonald & Zuckerman, 1962; Potter & Schild, 1967; Tyrrell, Sparrow & Beare, 1968; Potter, 1969; Cuadrado & Davenport, 1970; Evans, Shepard & Richards, 1972; Mackenzie & Fimmel, 1978). The methodological problems inherent in these studies brought Evans *et al.* (1972) to suggest a series of conditions for a meaningful study of this topic. These criteria form a basis for comparisons between different studies, and their fulfilment is considered essential for drawing valid conclusions.

An influenza A(H_1N_1) outbreak in a recruit base in the Israel Defence Forces (IDF) in February 1978, which met most of the criteria, appeared to provide an excellent opportunity for a study of this relationship.

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METHODS

The characteristics of the population, the outbreak and the clinical and serological outcomes are described in greater detail elsewhere (Lebiush, Rannon & Kark, in the press). Briefly, the population consisted of 336 healthy male recruits aged 18·5 ± 0·7 years (mean ± S.D.) with a range of 17–24 years. Only four subjects were aged 20 or more. An explosive and sharply delineated outbreak of influenza-like illness occurred at the end of February 1978, and continued for two and a half weeks. Seventy per cent of the cases reported during a seven-day period. The symptomatology was generally mild; fever exceeded 38 °C in one-half of the cases. An influenza A virus, similar to A/USSR/90/77 (H_1N_1) was isolated in 5 of 22 acutely ill patients from whom nasopharyngeal swabs were taken. We found this virus far more difficult to isolate than previous subtypes. Using conventional serological methods (US Department of Health, Education and Welfare, 1975), all 22 recruits were found to lack haemagglutination inhibiting (HI) antibodies to A/USSR/90/77 antigen during the acute phase. Sixteen of the 18 patients, for whom paired sera were available, sero-converted from titres of less than 10 to between 10 and 80. This was taken as evidence that the sharp outbreak was due to an influenza A strain closely related to A/USSR/90/77 (H_1N_1). This was one of the first isolations in Israel of H_1N_1 virus following the disappearance of this subtype over 20 years ago. Prior to 1978 no H_1N_1 virus had been detected. Our study population, born after 1957, was thus entirely susceptible.

Approximately two months after the outbreak, sera from 323 of the 336 recruits were tested for HI antibodies against A/USSR/90/77 (H_1N_1) and A/Texas/1/77 (H_3N_2) antigens. Titres were examined at an initial dilution of 1:10. A titre of less than 10 was deemed negative and defined as 5 for purposes of calculating geometric mean titres (GMT). We assumed that all recruits lacked antibody to H_1N_1 prior to the outbreak; therefore, any HI titre $\geqslant 10$ against H_1N_1 was considered as serological evidence of infection.

Data relating to clinical morbidity were gathered from the unit medical records, in which all visits to a physician or medical corpsman were routinely recorded. As all sick recruits were required to visit only their own unit clinic, and as training was stopped during the outbreak and all ill recruits, even with mild symptoms, were encouraged to visit the clinic, we believe that most clinical cases of influenza were included in this study. Each recruit that reported to the clinic with respiratory symptoms during the 17-day period of the outbreak was defined as a clinical case. A total of 58% of the exposed population (196/336) became clinically ill.

ABO blood groups were routinely examined at the Israel Defence Forces induction centres a year earlier and were retrieved from computer storage.

RESULTS

The frequency distribution of blood groups among the 336 recruits was as follows: 32·8% were group O, 38·4% were A, 22·3% were B and 6·5% were AB. These frequencies are similar to those for a large sample of Israel Defence Forces inductees examined during the same year, in whom 35·1% were O, 36·8% were A,

Table 1. *The proportion of clinical influenza among the different ABO blood groups in the study population*

Blood group	Number ill	Number exposed	Percentage ill
O	61	110	55·5
A	80	129	62·0
B	45	75	60·0
AB	10	22	45·5
Total	196	336	58·0

$\chi^2 = 2{\cdot}7$, degrees of freedom (D.F.) = 3, $P = 0{\cdot}44$.

Table 2. *Comparison of post-epidemic HI antibody titres to A/USSR/90/77 (H_1N_1) and blood groups in 323 recruits*

Blood group	Total number	Number (percentage) with HI titres of					
		< 10	10	20	⩾ 40	⩾ 10	⩾ 20
O	105	50 (47·6)	31 (29·6)	14 (13·3)	10 (9·5)	55 (52·4)	24 (22·8)
A	125	49 (39·2)	24 (19·2)	36 (28·8)	16 (12·8)	76 (60·8)	52 (41·6)
B	71	30 (42·3)	13 (18·3)	20 (28·2)	8 (11·3)	41 (57·7)	28 (39·4)
AB	22	7 (31·8)	13 (59·1)	1 (4·5)	1 (4·5)	15 (68·2)	2 (9·1)

Considering individuals with HI titres ⩾ 10: $\chi^2 = 2{\cdot}7$, D.F. = 3, $P = 0{\cdot}44$ (not significant). Considering individuals with HI titres ⩾ 20: likelihood ratio $\chi^2 = 17{\cdot}575$, D.F. = 3, $P = < 0{\cdot}001$. With multiple comparisons to determine in which part of the table the differences lie (D.F. = 3): $P = < 0{\cdot}01$ for (O + AB) versus (A + B); $P = < 0{\cdot}02$ for O versus (A + B), AB versus (A + B) and AB versus A; $P = < 0{\cdot}05$ for O versus A and AB versus B; not significant for O versus AB, A versus B and O versus B.

20·4% were B and 7·6% were AB. No significant difference was evident for the different ethnic groups, but ethnic-specific numbers were rather small in our sample.

No significant difference between rates of clinical influenza was seen for the different blood groups. These ranged between 45·5% and 62% (Table 1).

The proportion of subjects with a post-epidemic titre of ⩾ 10 did not differ significantly in the various blood groups (Table 2). However, the percentage of subjects with a post-epidemic titre of ⩾ 20 was significantly lower in groups O and AB (22·8% and 9·1% respectively) than in groups A and B (41·6% and 39·4% respectively). Group O did not differ significantly from group AB. In contrast, a greater proportion of group AB (59·1%) and group O (29·6%) had a post-epidemic titre of only 10 compared with groups A and B (19·2% and 18·3% respectively).

We were unable to explore adequately the differential distribution of antibody at titres 40 or greater in the blood groups because only 35 subjects responded to these levels. Differences between the blood groups were in the same direction but were small and not statistically significant.

The geometric mean antibody titres (GMT) of the four blood groups were compared. A titre of < 10 was calculated as equal to 5. The GMT for groups O, A, B and AB were 9·1, 11·5, 10·5 and 9·0 respectively. The *F* test for difference in means between the blood groups (analysis of variance) did not reach conventional

Table 3. *The distribution of serologically confirmed clinical influenza (titre ⩾ 20) by ABO blood group*

Blood group	Total number	Serologically confirmed clinical influenza	
		Number	%
O	105	20	19·0
A	125	42	33·6
B	71	22	30·1
AB	22	1	4·5

Likelihood ratio $\chi^2 = 14{\cdot}441$, D.F. = 3, $P < 0{\cdot}005$.

Partitioning total χ^2: $\chi^2 = 10{\cdot}783$, D.F. = 3, $P = < 0{\cdot}025$ for (O + AB) versus (A + B); not significant for A versus B and O versus AB.

levels of statistical significance ($P = 0{\cdot}085$). The ranking of the GMT is consistent with the proportions of the different blood groups responding at the different antibody levels. The GMT differences between the blood groups were small because the majority of the population either did not respond (titre < 10) or reached an antibody titre of only 10, while relatively few subjects reached higher antibody levels.

We examined serologically confirmed clinical influenza by blood groups (as done by McDonald & Zuckerman (1962) and Evans *et al.* (1972)) (Table 3). Again the excess morbidity in groups A and B as compared with O and AB stood out. The behaviour of group AB was especially striking.

As suggested by Evans *et al.* (1972), the proportion of clinical influenza among those that seroconverted to titres ⩾ 20 in the different blood groups was examined. There were no statistically significant differences. Influenza morbidity among recruits that seroconverted was 80 %, and was almost identical for groups O, A and B. In group AB there were too few observations to be useful.

DISCUSSION

Previous studies have been characterized by varying study designs, response criteria and influenza virus types. Thus it is difficult indeed to compare results. These data are summarized in Table 4.

McDonald & Zuckerman (1962) in a study of 701 ill recruits during an A(H_2N_2) influenza outbreak, found a greater incidence of clinical influenza, confirmed serologically or virologically, in blood group O than in A. Our study of an A(H_1N_1) outbreak does not confirm this finding.

Potter & Schild (1967) studied antibody levels to A(H_2N_2) in 515 subjects of different ages in 1961–3 and also demonstrated a greater prevalence of antibody titre of ⩾ 6 in blood group O compared to A. This was statistically significant, however, in only two age groups (16–20 and above 30). Tyrrell *et al.* (1968) examined 199 volunteers experimentally exposed to various viruses, including influenza B and A(H_2N_2). Laboratory-confirmed infections of influenza B were significantly more common in blood group O than in A, whereas more group A were clinically

ill than group O. Among 1500 recruits from three South American countries described by Cuadrado & Davenport (1970), antibody titres of $\geqslant 10$ against $A(H_1N_1)$ and $A(H_2N_2)$ were significantly more prevalent in groups O and B than in group A. In contrast, Potter (1969) found no difference among the ABO blood groups in prevalence of antibodies to $A(H_1N_1)$ and $A(H_2N_2)$ in samples drawn in 1966. He concluded that repeated exposure to an influenza subtype may mask differential susceptibility or response to influenza virus in the different blood groups, and thus cloud the issue. Therefore, Potter suggested that these relationships should be examined in a study population not previously exposed to the prevailing strain.

Accordingly, Evans *et al.* (1972) examined 276 Yale University students undergoing their first exposure to the $A(H_3N_2)$ subtype. No difference was seen in the blood groups either for seroconversion (defined as a fourfold increase in titre) or in serologically confirmed clinical cases.

Mackenzie & Fimmel (1978), however, found that seroconversion following an $A(H_3N_2)$ outbreak was significantly more frequent in group B than in groups A and O, in subjects with a titre of $\leqslant 48$ prior to the outbreak. The greater incidence of seroconversion in group B did not appear to be related to prior antibody titres.

The sample in the present study suited most of the criteria laid down by Evans *et al.* (1972). Clinical data, including mild cases, were very complete. Interestingly enough, the rates of clinical disease were quite similar to those described in similar previously unexposed populations (Meiklejohn, Eickhoff & Graves, 1980; WHO, 1978*a*). Serological responses were also similar to the experience of others (Meiklejohn *et al.* 1980; Glass *et al.* 1978). The population of recruits, aged 23 or less, had not previously been exposed to the $A(H_1N_1)$ subtype, either naturally or by immunization. This population was born after $A(H_1N_1)$ strains ceased to circulate (WHO, 1978*b*). Individuals with various blood types were equally exposed to the virus. The outbreak was sharply delineated and occurred over a brief period of 17 days.

In our data, no association was seen between all clinical influenza and blood groups. In contrast, however, a significant association was noted between blood group and seroconversion to antibody titres $\geqslant 20$ with groups A and B responding substantially more than O and AB, while O and especially AB converted to a titre of 10 more frequently than A and B. Indeed, response of the AB blood group was limited almost entirely to the 1:10 antibody level. These findings are in contrast to Evans *et al.* (1972) and only partly accord with Mackenzie & Fimmel (1978). In contrast to McDonald & Zuckerman (1962) and Evans *et al.* (1972), a statistically significant excess of serologically confirmed clinical influenza was noted in groups A and B as compared with O and AB. Similarly to Evans *et al.* (1972), we did not find a significant difference in clinical influenza among seroconverters in the different blood groups.

Due to the relatively low frequency of group AB in most populations, little data are available in the literature with which to compare the quite interesting findings in the present study relating to this blood group. We can only hope that sufficiently large sample sizes will be used in the future to facilitate exploration of this relationship.

Table 4. *Summary of studies of ABO blood groups and influenza*

Author (year published)	Date of study	Influenza type	Population	Criterion for comparing between blood groups	Significant results for ABO blood groups
McDonald & Zuckerman (1962)	1956–61	$A(H_1N_1)$ $A(H_2N_2)$ B	Military personnel admitted to sick quarters: 129 with influenza $A(H_1N_1)$; 701 with influenza $A(H_2N_2)$; 63 with influenza B	Distribution of blood groups among those with clinical influenza confirmed serologically (fourfold rise in titre) or virologically was compared to a large control group	O > A for influenza $A(H_2N_2)$ only
Potter & Schild (1967)	1961–3	$A(H_2N_2)$	515 subjects aged 1–30+ with blood group O or A	Prevalence of antibody titre $\geqslant 6$	O > A for two age groups only: 16–20 and $\geqslant 30$
Tyrrell, Sparrow & Beare (1968)	1961–8	$A(H_2N_2)$ B	199 volunteers experimentally inoculated with influenza virus: 50 received $A(H_2N_2)$; 149 received B	(1) Incidence of clinical illness	(1) A > 0; A + B + AB > O
				(2) Incidence of infection confirmed serologically (antibody rise) or virologically	(2) O > A, $P < 0{\cdot}10$; O > A + B + AB ($P < 0{\cdot}10$) more evident for blood group B
				(3) Incidence of clinical illness among those infected	(3) A > O ($P < 0{\cdot}10$); A + B + AB > O more evident for blood group B
Potter (1969)	1966	Various, including $A(H_1N_1)$ $A(H_2N_2)$	396 subjects of different ages with blood groups O and A	Prevalence of antibody titre $\geqslant 6$	Not significant

Table 4. (*Cont.*)

Cuadrado & Davenport (1970)	1964	Various, including $A(H_1N_1)$ $A(H_2N_2)$	1500 military recruits from 3 South American countries	Prevalence of antibody titre $\geqslant 10$	O, B > A
Evans, Shepard & Richards (1972)	(1) 1962–6	(1) $A(H_2N_2)$	(1) 650 young adults	(1) Incidence of infection confirmed serologically (fourfold or greater rise in titre)	All not significant
	(2) 1968	(2) $A(H_3N_2)$	(2) 276 Yale students during first exposure to virus in epidemic period	(2*a*) Incidence of infection confirmed serologically (2*b*) Incidence of clinical illness among those infected	
Mackenzie & Fimmel (1978)	1973–4	$A(H_3N_2)$	659 volunteers during $A(H_3N_2)$ epidemic	Incidence of infection confirmed serologically (fourfold or greater rise in titre)	B > O, A regardless of pre-epidemic titre

Findings from the present and previous studies lend support to hypotheses that genetic factors related to ABO blood groups may influence influenza morbidity or immune response (Muschel, 1966). Spencer, Cherry & Terasaki (1976) found that HL-A type BW 16 individuals are resistant to infection with a live attenuated influenza virus, adding information as to the genetic component determining the response.

The recent A(H_1N_1) epidemics should provide investigators with a useful opportunity to examine the consistency of the relationship between ABO blood group and influenza.

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REFERENCES

CUADRADO, R. R. & DAVENPORT, F. M. (1970). Antibodies to influenza viruses in military recruits from Argentina, Brazil and Colombia. Their relation to ABO blood group distribution. *Bulletin of the World Health Organization* **42**, 873–84.

EVANS, A. S., SHEPARD, K. A. & RICHARDS, V. A. (1972). ABO blood groups and viral diseases. *Yale Journal of Biology and Medicine* **45**, 81–92.

GLASS, R. I. M., BRANN, E. A., SLADE, J. D., JONES, W. E., SCALLY, M. J., CRAVEN, R. B. & GRESS, M. B. (1978). Community wide surveillance of influenza after outbreaks due to H_3N_2 and H_1N_1 influenza viruses. *Journal of Infectious Diseases* **138**, 703–6.

LEBIUSH, M., RANNON, L. & KARK, J. D. An outbreak of A/USSR/90/77 (H_1N_1) influenza in army recruits – clinical and laboratory observations. *Military Medicine*. (In the Press.)

MACKENZIE, J. A. & FIMMEL, P. J. (1978). The effect of ABO blood groups on the incidence of epidemic influenza and on the response to live attenuated and detergent split influenza virus vaccines. *Journal of Hygiene* **80**, 21–30.

MCDONALD, J. C. & ZUCKERMAN, A. J. (1962). ABO blood groups and acute respiratory virus disease. *British Medical Journal* **ii**, 89–90.

MEIKLEJOHN, G., EICKHOFF, T. C., GRAVES, P. & JOSEPHINE, I. (1980). An influenza A epidemic caused by H_1N_1 virus. *Military Medicine* 129–31.

MUSCHEL, L. H. (1966). Blood groups, disease and selection. *Bacteriological Reviews* **30**, 427–41.

POTTER, C. W. (1969). HI antibody to various influenza viruses and adenoviruses in individuals of blood group A and O. *Journal of Hygiene* **67**, 67–74.

POTTER, C. W. & SCHILD, G. C. (1967). The incidence of HI antibody to influenza virus A 2/Singapore/1/57 in individuals of Blood Groups A and O. *Journal of Immunology* **98**, 1320–5.

SPENCER, M. J., CHERRY, J. D. & TERASAKI, P. I. (1976). HL-A antigens and antibody response after influenza A vaccination. Decreased response associated with HL-A type W 16. *New England Journal of Medicine* **294**, 13–16.

TYRRELL, D. A. J., SPARROW, P. & BEARE, A. S. (1968). Relation between blood groups and resistance to infection with influenza and some picornaviruses. *Nature, London* **220**, 819–20.

UNITED STATE DEPARTMENT OF HEALTH, EDUCATION AND WELFARE (1975). Advanced Laboratory Techniques for Influenza Diagnosis. *Public Health Service, Immunology series*, no. 6.

WORLD HEALTH ORGANIZATION (1978*a*). Influenza Surveillance. *Weekly Epidemiological Record* **53**, 53–60.

WORLD HEALTH ORGANIZATION (1978*b*). Influenza Surveillance. *Weekly Epidemiological Record* **53**, 9–20.