Bull. Org. mond. Santé }
Bull. Wld Hlth Org. } 1973, **49**, 333-340

Trials of aqueous killed influenza vaccine in Canada, 1968–69*

M. C. WILLIAMS,[1] L. DAVIGNON,[2] J. C. McDONALD,[3] P. V. PAVILANIS,[4] A. BOUDREAULT,[5] & A. J. CLAYTON [6]

The appearance of the pandemic A/Hong Kong/1/68 (H3N2) influenzavirus strain provided an opportunity for a clinical field trial of influenza vaccines in Canada during the winter of 1968–69. As by November 1968 there were reports of influenza B activity and as supplies of A2/HK/68 vaccines were limited, it was decided to make a series of strictly randomized double-blind trials comparing A2/HK/68 vaccines not only with B/Mass/66 vaccines but also with a bivalent vaccine that was already in production and contained B/Mass/66 and A2/Mtl/68, the latter a strain isolated in Canada during January 1968. In 4 trials, a total of 13 729 military personnel and 4 795 primary schoolchildren were vaccinated. Reported vaccine reactions were less than 0.1% with zonally-purified vaccines and 2.6% with the "standard" aqueous killed bivalent vaccine. Three children had serious reactions. Surveillance detected an outbreak of influenza in the first two trials on the military. The 3 vaccines containing A2 strains gave similar clinical protection conservatively estimated at 42–55% but probably about 80%. The effectiveness of the A2/Mtl/68 vaccine, which was in production before the Hong Kong variant had been isolated, was unexpected. In the absence of a vaccine specific to a new pandemic strain, it should not be assumed that a vaccine made from another recent strain could not be useful.

Influenza is probably the most important single respiratory infection in Canada and accounts for about 1 000 deaths a year and 5% of all absenteeism from work (10).

The antigenic changes in influenzavirus A and the rapid pandemic spread of new variants make the production of sufficient vaccine from a new strain difficult to accomplish and limit the opportunities for its evaluation in a field trial. In addition, the protection provided by an influenza vaccine is difficult to estimate because of diagnostic problems in distinguishing influenzavirus infection from other causes of febrile illness.

The status of influenzavirus vaccines has been reviewed frequently (1, 7, 15, 19). In summary, the US Commission on Influenza has tended to base estimates of protection upon illnesses that were confirmed serologically. But as laboratory evidence of influenza may be harder to obtain in inoculated than in uninoculated groups (9), British studies have usually relied on clinical rather than laboratory diagnosis and thus probably underestimate the degree of protection. Aqueous killed vaccines may give at least 80% protection against only an antigenically similar virus, and the duration of protection may be prolonged by oil adjuvants.

For Canada the only published report of a major field trial was that carried out in 1954–55 by Pavilanis et al. in about 9 000 adults using a killed aqueous quadrivalent vaccine (12). It was estimated that the vaccine conferred protection varying between 40% and 80%; a further trial on adults and children was inconclusive as there was no outbreak of influenza.

* This study was assisted by a Canadian National Health Grant, Project 604-7-648.

[1] Formerly Professor, [2] Formerly Associate Professor, [3] Professor and Chairman, Department of Epidemiology and Health, McGill University, Montreal, Canada.

[4] Director of Science, [5] Virologist, Institute of Microbiology & Hygiene, University of Montreal, Montreal, Canada.

[6] Epidemiologist, Directorate of Preventive Medicine, Surgeon General's Office, Canadian Forces Headquarters, Ottawa, Canada.

Requests for reprints should be addressed to Dr J. C. McDonald, Dept. of Epidemiology and Health, 3775 University Street, McGill University, Montreal, Canada.

In 1968 a group from the Department of Epidemiology and Health, McGill University, and the Institute of Microbiology and Hygiene (IMH), University of Montreal, undertook a joint research programme into the epidemiology of influenza and the development and testing of influenza vaccines. By September 1968, a prolonged serological survey in five localities in the province of Quebec and a pilot trial to determine the potency of some commercially available vaccines were started. By the end of September, the influenza A2/Hong Kong/68 variant had become potentially pandemic, so plans were made for field trials. The limited availability of A2 Hong Kong vaccine led to the decision to use vaccine prepared from the A2/Mtl/68 strain that was already in production at the IMH. As it was uncertain that the Hong Kong variant would spread to Canada and as there were reports of influenzavirus B activity, it was decided to use a B/Mass/66 vaccine for comparison. In late November, the Vaccine Development Branch, U.S. National Institute of Allergy and Infectious Diseases also provided us with vaccines purified by zonal centrifugation.

MATERIALS AND METHODS

Preliminary trial

In a preliminary double-blind randomized antigenicity trial, 292 military recruits received one of four commercially available killed aqueous vaccines or a placebo control that were labelled A–E. There was considerable variation between the vaccines in the proportion of 4-fold HI (haemagglutination inhibition) rises to the different antigens. Most of this was correlated with the number of CCA units in each vaccine as shown in the accompanying tabulation.

Vaccine	*Klett-Summerson* CCA/ml (F 1.33)	*Pattern test* HA/ml (F 1.33)[a]
Standard IMH	2 053	38 400
A	308	10 214
B	266	7 661
C	618	15 321
E	60	2 554
D (placebo)	0	0

Vaccines

In the first clinical field trial on the military recruits, 2 aqueous killed vaccines, A2/Hong Kong/68 and B/Mass/66, were used. The vaccines, partially purified by zonal centrifugation (" zonally-purified "), were manufactured by Eli Lilly and Company, and contained 400 CCA units/0.5 ml.

In the other two trials on the military, 3 " standard " IMH aqueous killed vaccines were used, B/Mass/66, or A2/Hong Kong/68, or the bivalent B/Mass/66 and A2/Mtl/68.

In the trial with schoolchildren, only 2 standard IMH vaccines were used, either B/Mass/66 or A2/Hong Kong/68.

All vials containing vaccines were coded before dispatch in such a manner that the vaccinators did not know which type of vaccine was being used.

Vaccination. Military personnel were informed of the nature of the trial and invited to volunteer. Only healthy volunteers were vaccinated, while persons with a history of allergy to egg protein or receiving cortisone therapy were excluded. The names of volunteers and other identifying information were entered, in order of attendance, on vaccination registers that indicated by code letter the vaccine to be given. The allocation of vaccine codes was at random. All vaccines were inoculated subcutaneously into the left deltoid region. In the preliminary antigenicity trial, 1 ml was injected by means of individual disposable syringes. In the first military field trial 0.5 ml and in the other two 1.0 ml were inoculated, on all occasions using a jet gun. In the trial in children, 0.5 ml was inoculated using individual disposable syringes.

Volunteers

In the four studies the following groups were inoculated:

(*a*) Maritimes (25–28 Nov. 1968): 4 445 recruits of all ranks from 4 military bases—Greenwood (1 124), Bonaventure (508), Halifax (796), and Gagetown (2 017).

(*b*) Ontario I (9–13 Dec. 1968): 5 863 recruits of all ranks from 5 military bases—Toronto (753), Trenton (2 032), Kingston (1 207), Uplands (1 079), and Rockliffe (792).

(*c*) Ontario II (6–7 Jan. 1969): 2 971 recruits of all ranks from 2 military bases—Petawawa (2 061) and North Bay (910).

(*d*) Schoolchildren (9–10 Jan. 1969): 4 795 children from 10 primary schools throughout Montreal, for whose vaccination written and informed parental consent had been given.

[a] HA = haemagglutination; CCA = chick cell agglutination. F is the correction factor for the standard in the test to allow comparison with the NIH standard.

Follow-up

In the antigenicity trial, the men were closely observed for reactions and blood samples were taken for antibody tests before inoculation and again 1 and 2 months later. In each of the clinical trials with the recruits a small proportion of those vaccinated were randomly selected and bled at the time of vaccination and 2–4 weeks later to provide serum samples for antibody studies. For each person vaccinated, an individual record card was made and his sick parade record was marked to facilitate identification. For each reported illness, an individual illness record card was made with the following details: date of onset; diagnosis of influenza, other respiratory illness, or nonrespiratory illness; and the number of days absent from duty. For respiratory illnesses details of symptoms were recorded. A record was also kept of those in the trial who were transferred from the base. At each base, paired blood samples were collected throughout the trial, mainly from individuals with a respiratory illness, to obtain by antibody study an estimate of influenza activity. Military base surgeons were requested to report any outbreaks of influenza occurring during the vaccine trial. All 3 trials were terminated on 31 March 1969. Some bases were visited during the trials, and at the end of the trials all were visited by an epidemiologist who checked on the completeness and correctness of the recording procedures.

In the trial in schoolchildren, surveillance for 6 weeks commencing the week after vaccination was based on absence from school. Every day, a random sample of absent children was taken and, when necessary, nurses visited them to ascertain the cause of absence. Records were also made concerning any respiratory illness in the family. Every day, a similar random sample of children who were not absent was also selected for comparison and their homes were called to obtain information concerning respiratory illness in the family. Each week a small number of children with an acute febrile respiratory illness were visited within 24 hours of the onset to obtain samples of respiratory secretion for virus isolation.

Data handling

All editing and decisions concerning recorded data were made before analysis and without the knowledge of the vaccine group. At some bases nearly all vaccine reactions that led to absence from duty were classified as respiratory disease. The coded vaccine registers were not available to staff who made the follow-up records in any of the trials. The vaccine codes were broken when all analyses had been completed.

Laboratory tests

The blood samples were collected in Vacutainers, the sera being separated at the base camp and kept at 4°C until received at Montreal where they were stored at −20°C until tested.

Haemagglutination inhibition (HI) tests were carried out with microtitre equipment, 4–8 units of influenza antigen, and 1% fowl cells. Serum inhibitors were removed with a receptor destroying enzyme.

Complement fixation (CF) tests were also carried out with microtitre equipment. The antigens were supplied by the Federal Virus Laboratory, Ottawa, and the sera were heat-inactivated at 56°C for 30 min.

The isolation of influenzavirus was made in fertile hens' eggs and in primary rhesus monkey kidney cell cultures. Isolates were identified by HI tests with reference antisera supplied by the Federal Virus Laboratory, Ottawa.

RESULTS

Studies on the military recruits

Information on the vaccines given, the numbers vaccinated, and the numbers leaving the base may be seen in Table 1.

Vaccine reactions. In the preliminary study, only one man had a reaction that led to absence from duty. For the field trials the numbers of reactions reported during the 2 days after vaccination are shown in Table 1.

Serologic response to vaccines. In the field trials, paired serum samples were tested by HI tests against influenzaviruses A2/Mtl/68, A2/HK/68, and either B/Mass/66 or B/Can/66. Details of the geometric mean titre (GMT) antibody levels and the number of 4-fold rises may be seen in Table 2.

Evidence of influenza incidence. In the field trials, only one base (Kingston) reported an outbreak of influenza and 3 strains, identified as A2 Hong Kong, were isolated from men who became sick on 17 January 1969. Subsequently, when other bases in the Maritimes and Ontario I areas were visited

Table 1. Details of the three field trials with military recruits

Trial (dates inoculated)	Vaccine type [c]	No. vaccinated	No. transferred	All reactions reported on days 1 & 2	No. of new illnesses leading to absence from duty				
					All weeks			Epidemic weeks	
					No. of weeks	NRD [a]	RD [b]	No. of weeks	RD [b]
Maritimes (25-28 Nov. 1968)	B/Mass/66	2 214	137	2	18	63	181	5	103
	A2/HK/68	2 231	135	3	18	65	127	5	48
Ontario I (9-13 Dec. 1968)	B/Mass/66	1 955	15	11	16	47	203	5	118
	A2/HK/68	1 947	14	10	16	56	153	5	68
	B/Mass/66 A2/Mtl/68	1 961	20	46	16	51	173	5	65
Ontario II (6-7 Jan. 1969)	B/Mass/66	988	14	6	13	12	38	no epidemic	
	A2/HK/68	987	7	1	13	11	28	no epidemic	
	B/Mass/66 A2/Mtl/68	996	14	18	13	13	45	no epidemic	

[a] NRD = nonrespiratory disease.
[b] RD = respiratory disease.
[c] In the Maritimes the vaccines were zonally purified, whereas in Ontario I and II " standard preparations " were used.

it was found that influenza-like illnesses had been noted during January but not more than was expected for the season, so that no outbreak was reported. In Table 3 may be found the proportion of paired serum samples (from patients mostly sick with respiratory disease) that gave by CF or HI tests a 4-fold or greater rise to A2 influenza antigens.

Sickness in the trial groups. The numbers absent from duty with newly reported respiratory and nonrespiratory diseases are given in Table 1. In Fig. 1

Table 2. HI antibody response to vaccines used in the three field trials with military recruits. The pre-vaccination serum sample was taken at the time of vaccination and the post-vaccination sample 2–4 weeks later

Trial	Vaccine type	No. of paired sera	Geometric mean titre						No. of rises ⩾ 4-fold		
			A2/Mtl/68		A2/HK/68		B/Mass/66, B/Can/66 [a]		A2/ Mtl/68	A2/ HK/68	B/Mass/66 B/Can/66 [a]
			pre	post	pre	post	pre	post			
Maritimes	B/Mass/66	81	15	22	7	17	22	87	7	10	35
	A2/HK/68	76	14	57	9	97	24	26	33	53	4
Ontario I	B/Mass/66	41	67	107	7	29	2	17	6	14	23
	A2/HK/68	42	61	266	9	152	2	3	23	33	4
	B/Mass/66 A2/Mtl/68	37	72	714	7	37	1	25	27	21	26
Ontario II	B/Mass/66	27	49	57	5	15	3	76	1	9	19
	A2/HK/68	28	37	234	6	138	5	6	19	23	1
	B/Mass/66 A2/Mtl/68	22	39	185	3	27	3	119	17	15	21

[a] In the Maritimes trial the influenza B antigen used for testing was B/Can/66. In the two Ontario trials, a closely related antigen, B/Mass/66, was used.

Table 3. The proportions of influenza cases during the 1968-69 trials with military recruits, confirmed by serologic analysis

Trial	December	January	February	March
Maritmes	3/22[a]	49/89	21/57	1/12
Ontario 1	9/24	37/96	9/66	0/7
Ontario II	—	10/28	3/10	0/0[b]
Total	12/46	96/213	33/133	1/19

[a] The proportion of CF or HI fourfold or greater rises with paired sera in sick persons using A2/Mtl/68 and A2/HK/68 HI antigens and influenza A CF antigen.

[b] No paired samples received.

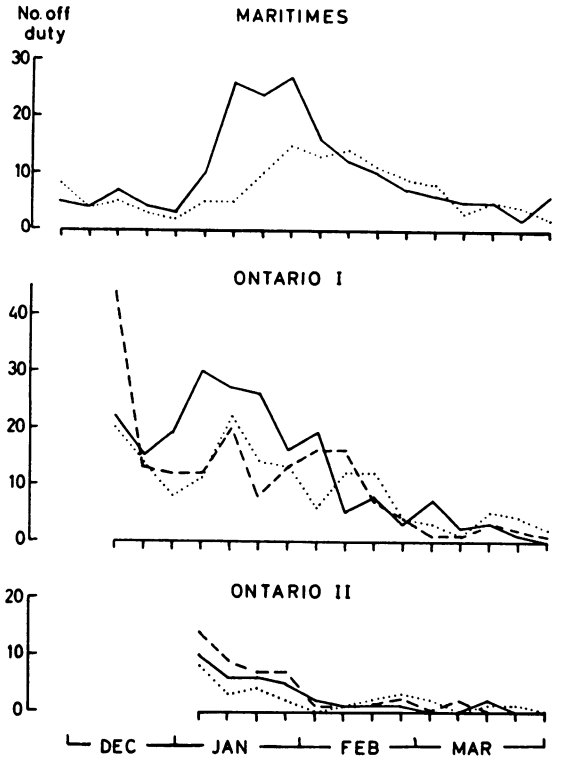

Figure 1. Clinical field trials on recruits from 3 military bases in 1968–69 showing the weekly numbers absent from duty owing to respiratory disease (solid line, B/Mass/66 vaccine; dotted line, A2/HK/68 vaccine; dashed line, bivalent B/Mass/66, A2/Mtl/68 vaccine).

the weekly number of men absent from duty with newly reported respiratory disease after vaccination in each trial may be seen. There was an epidemic throughout January in the Maritimes base and during the last week of December and January in the Ontario I base. In the Ontario II trial there was no epidemic wave. In both the Maritimes and Ontario I trials considerably more respiratory disease occurred in the group that received the " control " monovalent B vaccine.

A notable feature in Fig. 1 is the large number of absences during the first week of the Ontario I trial in the group receiving the bivalent vaccine. The large number of reactions recorded for this vaccine group (Table 1) suggested a relationship, and an examination of the illness record cards showed that nearly all vaccine reactions had been classified as respiratory disease.

Protection. The level of protection given by the vaccines was obtained by comparing the number of respiratory illnesses during the epidemic weeks, which appeared to be weeks 6–10 inclusive for the Maritimes and 3–7 inclusive for Ontario I (Table 1). From these totals, it may be calculated that the zonally-purified A2/HK/68 vaccine protected 52%, i.e., (103−48)/103, of subjects when compared with the B/Mass/66 " control "; and similarly that in the Ontario I trial with standard vaccines, the A2/HK/68 vaccine and the A2/Mtl/68 bivalent vaccine gave protection to 42% and 45% of subjects respectively, compared with the B/Mass/66 " control ".

These are underestimates, however, as they do not take into account the proportion of respiratory diseases that were not due to influenza. Two crude estimates of this proportion are available. The first may be obtained from Table 3, which shows that the proportion of influenza infections during January in the Maritimes base was 49/89 and in Ontario I was 37/96, giving estimates for non-influenzal respiratory disease of 45% and 61% respectively for these areas. Thus for the epidemic period in the Maritimes trial it may be estimated that 68 (45% of 151) of the respiratory illnesses leading to absence were not caused by influenza, the corrected values for influenza illness being 69 and 14 for the group receiving the B/Mass/66 or the A2/HK/68 vaccine respectively. This gives an estimate of 80% protection for the zonally-purified A2/HK/68 vaccine. With similar calculations it may be estimated that in the Ontario I trial the standard vaccines containing A2/HK/68 or A2/Mtl/68 gave protection to 79% and 84% of subjects respectively.

The other crude estimate of non-influenzal respiratory disease may be obtained by assuming that the respiratory illnesses occurring outside the epidemic period were not due to influenza and that their average weekly number was a reasonable estimate of their incidence. For the Maritimes base this weekly average was 12 and the absences due to influenza may be estimated as 73 (B/Mass/66) and 18 (A2/HK/68), an estimate of 75% protection being allowed for the zonally-purified A2/HK/68 vaccine. For the Ontario I trial, excluding the results for the first week since they included a considerable number of vaccine reactions reported as respiratory disease, the weekly non-epidemic average was 19.2. The estimates for absences during the epidemic period are therefore 85 (B/Mass/66), 35 (A2/HK/68), and 32 (A2/Mtl/68). From these corrected numbers it may be calculated that the protection offered by the A2/HK/68 and A2/Mtl/68 standard vaccines was 59% and 62% respectively.

Studies in schoolchildren

Reactions. In the field trial in primary school children there were 17 reactions reported, 10 being minor local reactions and 7 general reactions with a fever over 38.3°C. Three children in the latter group were admitted to hospital. One was a 7-year-old boy who had redness, pain, and oedema around both ankle joints. No cause for this swelling was found on thorough investigation, but he had a similar reaction a year previously after receiving a poliomyelitis vaccine of unknown type. The other two were a brother and sister who both had a high fever (41°C) and signs of meningeal irritation on the day after vaccination. Laboratory investigation revealed no cause for the illnesses, but both children recovered and were discharged 24 hours after admission to hospital.

Influenza prevalence. Throughout the 6-week surveillance period respiratory secretions were collected from 24 children with an influenza-like illness. Six strains of influenzavirus identified as similar to the Hong Kong variant were isolated, 2 during each of the 1st and 2nd weeks and 1 during each of the 4th and 6th weeks; 3 strains came from 14 children who had received the A2 vaccine, and 3 from 10 children who had received the B vaccine. Despite these isolations, the total respiratory absences averaged only 4% throughout the period. No significant differences in absences were found in the two vaccinated groups or in the occurrence of respiratory illnesses in their families. It was concluded that the trial was carried out too late to obtain evidence of protection.

DISCUSSION

In all these trials care was taken to eliminate bias by ensuring that they were double-blind with random allocation of subjects to vaccine groups. Some confirmation that randomization was successful within each trial may be found by comparing for each vaccine group the numbers who were vaccinated, transferred from the base, or absent from duty with a nonrespiratory disease (Table 1). In all 9 comparisons, the numbers are very close. In each trial the prevaccination serologic status for each vaccine group was also similar (Table 2).

Reported reactions (Table 1) with the zonally-purified vaccines were few (about 0.1%). With the standard monovalent vaccines, rates were higher but less than 1%; the bivalent vaccine gave a reaction rate of just over 2.6% presumably related to its larger antigen content. These results are in agreement with other studies on zonally-purified vaccines (5, 11, 13). Our figure of 2.6% reported reactions with the standard bivalent vaccine is within the expected range for this type of vaccine.

The 3 serious reactions in the children who received the standard vaccine were not exceptional, and Foy et al. reported that they also occurred with zonally-purified vaccines (6). Such results underline that children are particularly reactive to killed aqueous vaccines and emphasize the need for less toxic preparations for their protection.

In the field trials (Table 2), the geometric mean titre (GMT) of the preinoculation serum samples was high with A2/Mtl/68 in the Ontario studies and moderately high with B/Can/66 in the Maritimes population. There is evidence that the vaccines used were antigenically potent and administered according to the vaccine code. There also appears to be an antigenic relationship between A2/Mtl/68 and A2/HK/68.

In the field trials adequate laboratory surveillance of influenza was not possible. Selection of the " epidemic " weeks was mainly based upon the number of additional absences from duty with respiratory disease in the groups receiving the " control " monovalent B vaccine. Any bias in this selection was probably small because the weeks were chosen not only from the form of the epidemic curve, but also on serologic evidence of A2 influenza (Fig. 1, Table 4).

The estimates of 52–80% and 42–79% protection for the zonally-purified and standard monovalent

A2/HK/68 vaccines are similar to those found in field trials with killed aqueous vaccines during previous influenza epidemics. There have been few other reports of similar trials to estimate the clinical protection afforded by killed aqueous Hong Kong vaccines. In a small double-blind trial Schoenbaum et al., using 3 zonally-purified vaccines in 2 doses, obtained evidence that the higher dose gave 70% protection (14). Similar studies in some 3 500 elderly Californian residents provided estimates of 50–70% protection for the same vaccine in a high dose. The standard 300 CCA dose, however, did not provide significant protection for either adult group. Waldman et al., in a study involving approximately 2 100 adults in Florida, compared a standard monovalent A2/HK/68 vaccine and a standard bivalent vaccine containing A2/62 and A2/64 antigens using subcutaneous or aerosol routes of inoculation (18). A single subcutaneous dose of the A2/HK/68 vaccine gave protection to 55–83%. In a South African study where 1 254 Bantu factory workers received a standard A2/Aichi/2/68 vaccine and 413 received a placebo vaccine, about 80% protection was provided by the Hong Kong vaccine (2). In British studies in over 4 000 adults and schoolchildren, Tyrrell et al. compared standard killed vaccines made from A2/Eng/12/64 or A2/Eng/344/68 (a Hong Kong variant) and failed to show any convincing evidence of protection (17).

That the standard bivalent vaccine containing A2/Mtl/68 antigen should give protection (45–84%) of the same order as the monovalent A2/HK/68 vaccines prepared from a pandemic strain was unexpected. There appears to be only one other study where significant protection was reported for a vaccine prepared from an A2 strain isolated prior to the Hong Kong variant. Eickhoff and Meiklejohn, using A2/Ann Arbor/67, a strain closely related to A2/Mtl/68, in an adjuvant bivalent vaccine reported 54% protection in a student population at an air force base in Colorado (3). Waldman et al. (18) found that adults were protected (27–40%) by standard bivalent vaccines containing A2/Taiwan/1/64 and A2/Japan/170/62, but Schoenbaum et al. (14) failed to find any protection using vaccines containing the same virus strains. Thus vaccines already in production and containing A2 variants isolated 16–18 months before the A2/Hong Kong/68 virus was isolated sometimes gave significant protection.

It is apparent that studies during the Hong Kong pandemic have raised many questions concerning the basis of influenza immunity, antigenic variation, and control (4, 8, 16). More knowledge is required concerning the protective role of anti-neuraminidase antibodies and nasal secretions and there is very little understanding of the nature of avirulent strains.

It seems likely that killed vaccines will be improved and used on a wider scale during the next influenza epidemic but it is unlikely that they will ever provide effective international control. For this, live attenuated influenza vaccines appear to offer the only solution.

RÉSUMÉ

ESSAIS D'UN VACCIN ANTIGRIPPAL TUÉ EN SOLUTION AQUEUSE, AU CANADA, EN 1968-69

A la fin de septembre 1968, il existait une menace de pandémie grippale due au variant A/Hong Kong/1/68 (H3N2) et des plans ont été établis pour procéder à des essais pratiques de vaccination au Canada. Les stocks de vaccin A2/HK/68 étant limités, on a décidé d'utiliser aux fins de comparaison un vaccin déjà en cours de production préparé à partir des souches A2/Mtl/68 et B/Mass/66 ainsi qu'un vaccin B/Mass/66. A la fin de novembre, on a également pu disposer d'une certaine quantité de vaccin A2/HK/68 purifié par centrifugation de zone.

Après des essais d'antigénicité préliminaires, on a organisé 4 essais de vaccination à double insu. Au total, 13 279 volontaires des forces armées et 4795 écoliers ont reçu soit un vaccin tué purifié par centrifugation de zone (B/Mass/66 ou A2/HK/68) soit un vaccin standard (B/Mass/66 ou A2/HK/68) soit un vaccin bivalent B/Mass/66 et A2/Mtl/68. L'observation du personnel militaire a comporté l'enregistrement détaillé des réactions postvaccinales, des cas de grippe et des absences de service ainsi qu'un contrôle sérologique de l'efficacité des vaccins.

Les réactions postvaccinales ont été peu nombreuses: moins de 0,1% avec les vaccins purifiés et 2,6% avec le vaccin standard bivalent. Trois enfants ont présenté d'importantes réactions. Tous les vaccins ont fait preuve de leur efficacité immunologique. On a enregistré une épidémie de grippe de Hong Kong parmi le personnel militaire participant aux deux premiers essais, mais aucun signe d'activité grippale n'a été constaté lors du 3e essai et du 4e organisé parmi les écoliers.

Durant la poussée épidémique, les trois vaccins préparés à partir de souches A2 ont conféré une protection

clinique similaire qu'une estimation prudente chiffre à 42-55% mais qui a dû atteindre en réalité 80%. Contre toute attente, le vaccin contenant la souche A2/Mtl/68 précédemment isolée a fait preuve d'une efficacité identique à celle obtenue après emploi du vaccin contenant la nouvelle souche épidémique A2/HK/68. Selon les auteurs, en l'absence d'un vaccin spécifique contre une nouvelle souche pandémique, on ne peut affirmer qu'un vaccin à base de souches récentes ne sera d'aucune utilité.

REFERENCES

1. DAVENPORT, F. M. *In*: First International Conference on Vaccines against Viral and Rickettsial Diseases of Man, Washington, D.C., 1966. Washington, Pan American Health Organization, 1967, p. 3.
2. EDDY, T. S. & DAVIES, N. A. *South African med. J.*, **44**: 214 (1970).
3. EICKHOFF, I. & MEIKLEJOHN, G. *Bull. Wld Hlth Org.*, **41**: 562 (1969).
4. FAZEKAS DE ST GROTH, *Arch. env. Hlth*, **21**: 293 (1970).
5. FINKLEA, J. F. ET AL. *J. infect. Dis.*, **120**: 708 (1970).
6. FOY, H. M. ET AL. *Bull. Wld Hlth Org.*, **41**: 564 (1969).
7. HIMMELWEIT, F. *Brit. J. clin. Pract.*, **17**: 661 (1963).
8. KILBOURNE, E. D. *Arch. env. Hlth*, **21**: 277 (1970).
9. MCDONALD, J. C. & ANDREWS, B. E. *Brit. med. J.*, **ii**: 1232 (1955).
10. MCDONALD, J. C. *Canad. med. Ass. J.*, **97**: 522 (1967).
11. MOSTOW, S. R. ET AL. *Bull. Wld Hlth Org.*, **41**: 525 (1969).
12. PAVILANIS, V. ET AL. *Canad. med. Ass. J.*, **79**: 527 (1958).
13. PHILIPPS, C. A. ET AL. *J. infect. Dis.*, **122**: 26 (1970).
14. SCHOENBAUM, S. C. ET AL. *Bull. Wld Hlth Org.*, **41**: 531 (1969).
15. STUART-HARRIS, C. H. *Proc. roy. Soc. Med.*, **60**: 659 (1967).
16. STUART-HARRIS, C. H. *Arch. env. Hlth*, **21**: 276 (1970).
17. TYRRELL, D. A. ET AL. *J. Hyg. (Lond.)*, **68**: 359 (1970).
18. WALDMAN, R. H. ET AL. *Bull. Wld Hlth Org.*, **41**: 543 (1969).
19. ZHDANOV, V. M. *In*: First International Conference on Vaccines against Viral and Rickettsial Diseases of Man, Washington, D.C., 1966. Washington, Pan American Health Organization, 1967, p. 9.