SESSION III

INACTIVATED INFLUENZA VIRUS VACCINES

Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1969, 41, 495-496

Production and Testing in the USA of Influenza Virus Vaccine Made from the Hong Kong Variant in 1968–69

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The Division of Biologics Standards of the National Institutes of Health made the Hong Kong variant of influenza virus available to US manufacturers for study in August 1968 and provided them with the Aichi strain for production purposes on 9 September. The first lot of vaccine was released on 15 November; 15 million doses had been released by the peak of the epidemic, which occurred in the first week of January 1969 in the USA, and 20 million doses by the end of that month. Despite the tremendous effort made, however, it is questionable whether the use of the vaccine, necessarily in smaller quantities than the total released, had any detectable effect on the course of the 1968–69 epidemic. The author suggests that it is also doubtful whether the 1957 epidemic of Asian influenza in the USA was significantly affected by the larger amount of vaccine that was then available before the epidemic peak was reached. He stresses that priority must be given to research into the problem of making sufficient vaccine available in good time to counter a threatened influenza epidemic.

Influenza vaccine, because of the changing character of the virus, presents problems almost every year. I do not need to describe these problems, which are covered in considerable detail in a number of the presentations at this Conference. During the fall of 1968 they became a matter of unusual concern to those involved in vaccine production and control because of the emergence in the Far East of a highly divergent A2 virus strain, the Hong Kong variant. In mid-July, an increase in respiratory illness was noted in Hong Kong and reported in the press. (It is of some interest that this mode of reporting gives us our first clue of some new development. Our first indication that something new was happening in 1957 was through press reports of respiratory disease outbreaks in the Far East.) Isolation of viruses was made in Hong Kong and cultures were expeditiously transmitted to laboratories in different parts of the world for study. By 13 August 1968, there was general agreement among virologists that these cultures differed markedly in character from the A2 strains which had been prevalent in recent years. The change was so marked that the ultimate development of an epidemic was clearly predictable since the vaccines available at that time could be expected to provide no more than limited protection, if any.

Knowing that the normal lead time for production of influenza virus vaccine is 4–5 months, the Division of Biologics Standards of the National Institutes of Health in the USA immediately provided cultures of this Hong Kong variant to the US vaccine manufacturers so that they could study its properties and determine whether a vaccine could be produced from it which would provide protection against the Hong Kong strain of influenza. Manipulation of influenza virus is often a lengthy and troublesome process since a new strain must be adapted to grow in fertile hens' eggs through an unpredictable number of generations or " passages ". While this work was in progress, a new isolate of the virus was received from Japan—the Aichi strain. This quickly showed a superior vaccine production potential and made possible a foreshortening of the work which had to be done prior to the actual initiation of vaccine production on a large scale. This strain was provided to the manufacturers on 9 September 1968 by the Division of Biologics Standards. Testing methods and procedures were worked out by the Division's

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scientists, and results, particularly those related to potency, were correlated in numerous conferences and laboratory demonstrations and workshops with the manufacturers. In order to expedite availability of vaccine, it was decided to base releases on the CCA content of a monovalent vaccine which was set at 400 units, and to perform all tests concurrently with those of the manufacturers.

The first lot of Hong Kong influenza vaccine, containing 110 000 doses, was released on 15 November 1968. In the ensuing weeks additional lots were produced and released as follows:

Date	*Cumulative total doses*
2 Dec. 1968	2 536 500
6 Dec. 1968	4 350 000
16 Dec. 1968	6 029 000
20 Dec. 1968	9 300 000
30 Dec. 1968	10 130 500
3 Jan. 1969	15 329 600
10 Jan. 1969	16 104 600
21 Jan. 1969	19 224 100
27 Jan. 1969	19 634 645
31 Jan. 1969	20 934 645

After January the demand for vaccine slackened and manufacturers began to phase out production. Even so, there was a considerable amount of unused vaccine after the peak of the epidemic had passed. Some of this became available for use in the southern hemisphere.

It is of interest to compare this performance with the situation which arose in 1957 when the Asian or A2 strain of influenza virus appeared. A comparison of the rate of availability of vaccine in these two situations, on a time-scale of days, is as follows:

	Days	
	1957	*1968*
Production strain available . . .	0	0
Requirements established	55	15
First batch released	94	66
First 5 million doses released . .	120	87

This comparison is even more illustrative of the effort involved when it is realized that the 1957 vaccine was only of half the strength of the 1968–69 vaccine during the time period covered by this summary.

A great deal of interest was expressed in the availability of vaccine by the lay and medical press as well as by many public figures. It was assumed by many when announcement of the first production lots was made that large amounts of vaccine would be available. It was difficult to explain that vaccine manufacture is a batch process and that many factors were involved (availability of eggs, personnel, equipment, etc.) and that there was really no sound way of judging what the market demands would be—a very important commercial consideration since it involves the disposition of capital funds. In 1957 a considerable surplus remained after the epidemic had subsided. One of the problems is that people and their physicians do not abide by the official recommendations for use, so that many people who really do not need vaccine receive it, while others in the high-risk group do not. Although the production of vaccine presents a great many problems, distribution in the face of an epidemic is the most difficult and is almost unsolvable. Despite this, manufacturers and most physicians in the USA generally worked very hard to adhere to the Public Health Service recommendations that first supplies of the vaccine be used exclusively for persons at highest risk. It is estimated that a considerably higher percentage of the priority group received the new Hong Kong vaccine in 1968–69 than in 1957 during the Asian influenza epidemic.

In 1957 the epidemic peaked in the USA during the second week in November, almost 6 months after the production strain became available. At this point 49 million doses had been released. Obviously, because of distribution and other delays, the amount used prior to the epidemic peak was much less than this. If we take into account the time required to build up antibodies, the number of people effectively immunized was relatively small. In 1968–69 the peak, determined retrospectively from mortality charts, occurred during the first week of January 1969, less than 4 months after the production strain became available.[1] At this time, which was sooner in relation to the available production time than in 1957, 15 million doses had been released. Thus, despite the tremendous effort made by all who were involved, it is questionable whether the use of vaccine had any detectable effect on the epidemic in either instance. Solutions are certainly needed and should be given a high priority in respiratory virus research during the coming decade. As we see it, this Conference should provide some of the documentation that can be used to assess the basic problem of vaccine availability in the face of a threatened epidemic.

[1] Two doses were probably needed but this would have represented an almost impossible situation.