

Study on the Impact of Public Health Measures on the Vaccine Phase III Clinical Trial Period

Ruyun Wang^{1,2,*}

¹Key Laboratory of Marine Hazards Forecasting, Ministry of Natural Resources (MNR), Hohai University, Nanjing, China;

²College of Oceanography, Hohai University, Nanjing, China.

Corresponding author: Ruyun Wang

Received: February 24, 2022

Published: March 08, 2022

Abstract

We derived the ratio of the period of time required for phase III trials for all vaccines in areas with and without public health interventions. The ratio is directly controlled by the public health protection rate, the greater the public health protection rate, the greater the proportion; When the public health protection rate tends to 1, this ratio tends to infinity.

Keywords: Public health measures; Vaccine; Phase III clinical trial; Trial period

Introduction

Phase III vaccine trials typically involve double-blind trials that divide large groups of people into control and vaccination groups. Unblinding was performed when the number of patients in the control group and vaccine group reached the required number of statistics. The incidence rates of the control and vaccination groups were calculated, as well as the current vaccine protection rate¹. It often takes years to meet the unblinding requirements for phase III vaccine trials, which is costly and risky for R&D organizations. Wang Ruyun (2021) studied the intermediate unblinding conditions and protection rate of phase III trial of COVID-19 vaccine, and preliminarily pointed out that protective measures (public health measures) have an impact on the vaccine phase III trial period². Based on previous work on phase III trials of COVID-19 vaccines, we derived the ratio of time periods required for phase III trials for all vaccines in areas with and without public health measures. The ratio is directly controlled by the public health protection rate, the greater the public health protection rate, the greater the proportion; When the public health protection rate tends to 1, this ratio tends to infinity. Thus, the internal influence of public health measures on the phase III trial period of vaccine was revealed. This suggests that phase III trials of vaccines should be conducted in areas where public health protection requirements are not high if unblinding requirements are to be met as quickly as possible. At the same time, it also reminds us that there may be problems with the currently used indicators for evaluating the effectiveness of vaccine protection and the eligibility criteria for testing vaccines.

Vaccine-related protection rate and evaluation criteria of qualified vaccines

Assume that the number of participants in the phase III vaccine

trial is m in both the control and vaccination groups.

In areas where no public health measures were taken, the number of cases in the control group and the vaccination group were respectively marked as $m_{c/n}$, $m_{v/n}$, and the incidence of cases in the control group and the vaccination group was respectively

$$r_{c/n} = m_{c/n}/m, r_{v/n} = m_{v/n}/m \quad \text{----(1)}$$

The corresponding rate $b_{v/n}$ of vaccine protection in areas where no public health measures have been adopted is

$$b_{v/n} = 1 - \frac{r_{v/n}}{r_{c/n}} \quad \text{----(2)}$$

In areas where public health measures were taken, the number of cases in the control group and the vaccination group were recorded as $m_{c/p}$, $m_{v/p}$ and the incidence of cases in the control group and the vaccination group were respectively

$$r_{c/p} = m_{c/p}/m, r_{v/p} = m_{v/p}/m \quad \text{----(3)}$$

The corresponding rate $b_{v/p}$ of vaccine protection in areas with public health measures is

$$b_{v/p} = 1 - \frac{r_{v/p}}{r_{c/p}} \quad \text{----(4)}$$

Suppose that the incidence of disease in a region without public health measures is r_n , and the incidence of disease after public health measures is r_p , then the protection rate b_p of public health measures is

According to the World Health Organization, the qualifying

$$b_p = 1 - \frac{r_p}{r_n} \quad \text{----(5)}$$

standard for vaccine protection is

$$b_{v/n} \geq 50\%, b_{v/p} \geq 50\% \quad \text{-----(6)}$$

The impact of public health measures on the phase III trial period of vaccines

Since phase III vaccine trials are usually unblinded when a set statistically significant number m_0 of infected persons has been reached, the unblinding period required for the trials in areas where no public health measures were adopted and where public health measures were adopted were T_n, T_p , respectively, and the time unit and the time period unit of incidence were both months.

The following studies were based on the assumption that the incidence would be the same in the absence of public health measures in different areas of the phase 3 vaccine trials.

Can be obtained by formula (1)-(4)

$$m_{c/n} = m \times r_{c/n} \quad \text{-----(7)}$$

$$m_{v/n} = m_{c/n} \times (1 - b_{v/n}) \quad \text{-----(8)}$$

$$m_{c/p} = m_{c/n} \times (1 - b_p) \quad \text{-----(9)}$$

$$m_{v/p} = m_{c/p} \times (1 - b_{v/p}) \quad \text{-----(10)}$$

The unblinding conditions of the trial in areas where no public health measures were taken were

$$m_{c/n} + m_{v/n} = m_0$$

Can be obtained according to formula (7) and (8)

$$mr_{c/n}(2 - b_{v/n}) T_n = m_0 \quad \text{---- (11)}$$

The unblinding conditions of the regional trials with public health measures were

$$m_{c/p} + m_{v/p} = m_0$$

Can be obtained according to formula (9) and (10)

$$mr_{c/n}(1 - b_p)(2 - b_{v/p}) T_p = m_0 \quad \text{----- (12)}$$

It can be derived from formula (11) and (12)

$$T_p / T_n = \frac{1}{1 - b_p} \frac{2 - b_{v/n}}{2 - b_{v/p}} \quad \text{-----(13)}$$

Assuming requirements $b_{v/p} = b_{v/n} = 50\%$ requirements of conformity, then

$$T_p / T_n = \frac{1}{1 - b_p} \quad \text{-----(14)}$$

Based on the results of the above formula, we give the following table 1.

Table 1: T_p/T_n under different public health measures.

b_p (%)	10	20	30	40	50	60	70	80	90
T_p / T_n	1.11	1.25	1.43	1.67	2	2.5	3.33	5	10

As can be seen from Table 1, phase III vaccine trials in areas with better public health practices require longer unblinding times than those in areas with no public health practices. Assuming that the unblinding time required in a region with no public health interventions were 3 months, the phase 3 trial in $b_p = 80\%$ would take 15 months.

By comparing the left side of Formula (11) and (12), it can be found that due to the intervention of public health measures, the number of cases decreased by a factor $(1 - b_p)$ of two in the same period, and the larger b_p , the more the decrease, so it is necessary to increase the trial period.

In addition, it can be seen from the left end of formula (11) and (12) containing factors $2 - b_{v/n}$ and $2 - b_{v/p}$, the larger $b_{v/n}, b_{v/p}$, the lower the number of patients, thus increasing the time of phase 3 trial. The more protective the vaccine, the longer the trial period. However, due to

$1 \leq 2 - b_{v/n} \leq 2$ and $1 \leq 2 - b_{v/p} \leq 2$, the effect on the trial period is limited, which is at most twice the unblinding time required in the case of complete vaccine failure.

References

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