Review Article

Metaanalysis of Vaccine efficacy for Monkeypox according to clinical criteria of history taking and clinical features and laboratory investigation

Abstract

Monkeypox virus is DNA virus of Orthopoxvirus. The Monkeypox is zoonosis disease first diagnosis in the Democratic Republic of the Congo in 1970 and originally transmitted from Vertebrate Reservoir. In 1796, Edward Jenner was the first physician achieved vaccine through exposing James Phipps to smallpox after immunization. The current study revise the vaccine efficacy and mortality rate of monkeypox. It is mainly transmitting from Squirrels to human providing mortality rate ranging from 2.7 to 10.1%. Globally, it estimated 4.4% the mortality rate of Monkeypox cases. Based on current review study, the effectiveness of smallpox vaccine in preventing the monkeypox is quite variable due to several selective clinical cases criteria such as history taking and clinical features and laboratory investigation, which modify the statistical result of the vaccine efficacy. The current study clarify the faults of calculation by elimination of several reasons and estimate the effectiveness of vaccine in the household Vaccine efficacy is 16.3% whereas total Vaccine efficacy is 0.6%. Using preventive measurement is first line to avoid infection therefore healthcare workers must adhere to precautions. Current study warns scientist to create monkeypox vaccine rather than depending on smallpox vaccine effectiveness due to lacking effectiveness vaccine and treatment.

Keyword: Monkeypox, Smallpox, Orthopoxvirus, Poxviridae, Mortality, Endemic, Africa

Introduction

Monkeypox virus is a double stranded DNA virus of Orthopoxvirus genus of Poxviridae family [1]. The first case of Monkeypox virus diagnosis was in cynomolgus monkeys in a laboratory setting in Copenhagen, Denmark in 1958 [2]. Later, the first human case was diagnosed in nine months child in the Democratic Republic of the Congo in 1970 [2]. In animal, there are different Vertebrate Reservoir in which Squirrels found to be the main reservoir. In 1796, Edward Jenner was the first treating physician achieved Vaccine through exposing James Phipps to smallpox after immunization [3]. The current review study discussed the vaccine efficacy and mortality rate of monkeypox. The world health organization has reported twenty-eight suspected and ninety-two confirmed cases of monkeypox in 12 non-endemic countries May 21 [4]. On August 2022, over monkeypox distributed over eighty-seven countries globally recording above 25,000 confirmed cases [5].

Method

The literatures linked to monkeypox are attained from PubMed and Google Scholar database. On PubMed there are 89 articles and on google scholar are 1300 articles. On The entire articles have been published in 2020 found to be almost 390 hundred articles. The entire articles are founded and selected based on the keyword 'Smallpox, Orthopoxvirus, Poxviridae, Mortality, Edward Jenner and monkeypox virus. The articles are selected only in English language. The data is collected and analysis via Statistical Package for the Social Sciences (SPSS).

Result

The current study reviews 10980-suspected cases, which are 1504 confirmed cases. It includes revision of different studies of different countries Cameron, Central African Republic, Democratic Republic of the Congo (DRC), Democratic Republic of the Congo (DRC) and Nigeria. The current studies estimated the death rate range from 2.7% to 33.3% with correct global mortality rate of confirmed cases 4.4% (Table 1)

Discussion

Monkeypox case diagnosis in the Democratic Republic of the Congo in 1970 [2] in which transmitted main by Squirrels. The monkeypox is zoonosis disease transmitted from human to human. In 97 animal cases study, monkeypox virus found to be in African Rope Squirrels in 26.8% whereas Squirrels West Africa Democratic of Republic Congo (DRC) in 19.59%. Further, the transmission of monkeypox from Gambian Giant Rat Africa and Midwest US (Wisconsin) in 15.46% and Gambian Sun Squirrel (heliosciurus spp.) in DRC 7.22% whereas Sooty Mangabey (cercocebusatys) in 5.15% and Dormice Africa in 5.15%. In addition, the transmission of monkeypox from Prairie Dog Indiana (Wisconsin) and "Bushmeat" found to be in 3.09% whereas Giant Anteater, Giant Pouch Rat and Thomas's Rope Squirrel (F.anerythrus) found in 2.06%. Yet, the transmission of monkeypox from Hedge Hog Africa, Jerboa Africa, Opossum Africa, Woodchuck Africa, Antelope, African Civet, Cricetomys and Graphiurus in 1.03%. Therefore, the most responsible reservoir is squirrels. It has direct transmission in 83.33%, aerosol in 8.33% and Fomite in 0.33% [6]. It may be transmitted from the animal to humans (primary zoonotic transmission), from humans to humans via bodily respiratory droplets, fluids such as blood, salivary skin lesion [7, 8]. In Series studies, sex intercourse is also transmission [9-12] found to be 83% of transmission monkeypox cases via gay or bisexual [12].

The clinical features of monkeypox are Headache, fever, chills, sore throat, rashes (macula, popular Vesicular, Pustular), Lymphadenopathy, Myalgia, Back pain, generalized malaise [13-15]. According to the incidence of clinical features, Rash (97%), Fever (85%), Chills (71%), Lymphadenopathy (71%), Headache (65%) and Myalgias (56%) [16]. In 1796, Edward Jenner was the first treating physician achieved Vaccine through exposing James Phipps to smallpox after immunization [3]. World health organization stated that the Smallpox Vaccine has effectiveness of preventing monkeypox in almost 85% according to revision of study done by Fine et al [7]. Fine and his team collect suspected 834 cases including 598 vaccinated and 236 unvaccinated cases in which 36 confirmed monkeypox cases including 10 vaccinated and 26 unvaccinated cases. Therefore, the attack rate of vaccinated and unvaccinated group are 0.017 and 0.110 respectively. According to practical guide for doctors, nurses, laboratory technicians, medical auxiliaries and logisticians [17], the vaccine efficacy usually calculated by three methods (Figure 1).

Based on the first method, the vaccine efficacy is a result of [(0.110-0.017)\0.110]x100 = [(0.093)\0.110] x 100 = [0.85] x100=85%

Based on the second method, the vaccine efficacy is a result of 100-(598-10)\ 598(1-10) =100-588\ 598(9) =100-(588\5382) = 100-10.9 (100-10.9) = 89.1% which mention as second vaccine efficacy for extradomiciliary contacts

Based on the third method, the vaccine efficacy is 85%, which is a result of (1-RR) x100= 1-(0.110-0.017) x100= (1-0.15) x100=0.85 x100= 85%

Therefore, the using of three different epidemiological method reaching the accurate percentage of 85% of smallpox vaccine efficacy to prevent monkeypox stated by world health organization based on fine et al [7] study. The main important questions regarding the vaccine efficacy is clinical questions have to be arising in current study. The vaccinated and unvaccinated groups were selected based on present and absent of scar in Fine et al [7] study. How the collector of sample differentiate the smallpox vaccine scar from other vaccine scar such as BCG. In 1964, 18 experts from WHO work to control the infection by estimating the price of BCG vaccine in Zaire [18]. In Zaire, Health services encouraged vaccination. Between 1971 and 1972, 1030709 smallpox and 214832 BCG vaccinations were performed respectively which double and ten time greater than number of vaccinations have been given during the period 1968-1970. (Zaire: Smallpox Cases by Month, (1968-1971) reported by World health organization [19]. In addition, study done by Arita et al [20] stated a rising reports of monkeypox cases with coexistent scar indicating vaccination. Moreover, Fine et al [7] assumed 70% of vaccinated group are actually receiving vaccine based on a history of vaccination in the past whereas Jazek et al [21] did not estimate the vaccine efficacy. The previous reasons hesitate the 85% vaccine efficacy clinically.

The history is not enough because the language barrier and low education found to be in rural area. The scar may indicate vaccination either smallpox or BCG immunization. Although, Smallpox is self-limited disease, which provide permanent immunity, the vaccinated and unvaccinated group may develop the infection with lack of laboratory work evidence and deficient material therefore the most of monkeypox cases diagnosed clinically rather than laboratory evidence in 1970s. Several concerns may arise regard method of collecting sample based on either history or scar presentation as an evidence of contact and vaccination.

Another study reported by Jezek et al [22] in Zaire between 1981-86, the data classified into vaccination and non-vaccination based on scar as well as the contact based on living and nonliving persons which are A total of 338 monkeypox patients out of 3686 contacts and infection rate found to be 12.7% of total number on Table 1. In current study, investigated more details to found the infection attack rate of 2657 vaccinated and 1029 non-vaccinate based on 43 and 295 vaccinated non-vaccinated infected of 388 found to be 1.62 and 28.7%. Based on vaccine efficacy formula, it found to be 94.4%. After revision of Jezek et al [22] study, he stated the secondary infection rate of affected village in vaccinated and unvaccinated group based on scar found to be 0.96% and 7.47% whereas the vaccine efficacy rate is 87.2% vaccine efficacy rate calculated on current study. In affected houses, the secondary infection rate in vaccinated and unvaccinated group found to 1.01% and 7.71% whereas the vaccine efficacy rate is 86.9%. Surprisingly, the unvaccinated people who is living in neighboring house less than person living in other houses does. Neighboring house may and may not have same contact risk to infected vaccinated or unvaccinated people. Therefore, the affected houses will provide more accurate infection rate and vaccine efficacy than the affected village. The previous percentages have not considered in Jezek et al [22] whereas only calculated in current study based on deficient points found in study method. Further, Jezek et al [22] study described that the sample collector in several visits every 7 to 10 days done by nurses and health inspectors who have less experience in history taking and clinical examination comparing to physicians beside the duration may create missing information between visits. Based on incubation period is ranging from 5 t0 21 days however typical incubation period of monkeypox virus infection is usually from 6 to 13 days therefore the missing date can occur due to the short duration of visit [1]. Also, the test are done by WHO Collaborating Centers for Disease Control in Atlanta, USA, and at the Research Institute for Viral Preparations in Moscow, skin sample examined by electron microscopy and cultured on chicken embryo chorioallantoic membrane and in tissue culture and serum sample. Specially, Anti-orthopoxvirus IgM indicates recent infection while IgG indicate either previous infection or vaccination [23]. Therefore, serum sample were to detect antibody, which may indicate previous infections or vaccination, which hesitate the result pf investigation in deciding infection, rather than vaccination.

In addition, Jezek et al [22] stated the secondary infection rate of vaccinated and unvaccinated group found to be 1.31% and 9.28 respectively whereas the current study found the vaccine

efficacy rate 85.9%. The vaccination efficacy of age group (0-4), (5-19), (10-14) and above 15 found to be 100%, 80.4%, 90.3% and impossible to determine. The impossible determine is due unable to have unvaccinated infective cases whereas the vaccinated infective cases presented indicating the scar present is BCG vaccine rather than smallpox vaccine. The peak of vaccine efficacy found to be 4 years and below when the vaccinated group is zero therefore, vaccine efficacy is inaccurate and incomparable to other age group. Five to nine and ten to fourteen year groups, the vaccinated group including two and one in number respectively that may provide misleading in infective attack rate and accuracy of vaccine efficacy.

Jazek et al [21] did not estimate the vaccine efficacy of affected house of vaccinated and unvaccinated members due to small number whereas the current study estimated 72.7%, which is the vaccine efficacy.

Further study, Jezek et al [24] clarified the investigation is according to presentation of vesicular and pustular fluid or scabs. It is two consecutive skin specimens within first week and third to fourth week. In addition, serum specimen is also collected in case of fade of skin rash. Further, blood specimens were collected from vaccinated contacts who had a history of recent fever, conjunctivitis, lymphadenitis, or other doubtful clinical features. On the other hand , Jezek et al [24] clarified 14 people had positive serology test without history evidence which is against the criteria of collecting sample however the positivity may indicate vaccination rather than infection. Jezek et al [24] divided the contacts based on living and nonliving house and selecting the secondary cases attack, which is 94% in both, which eliminate the contact reason therefore the vaccine efficacy is 87.5% in total 56 secondary cases contacts. In current study, several questions are raised of using the entire number of contact based on criteria of collecting sample to provide the attack rate leading to vaccine efficacy as well as the fourteen positive samples were collected which is against criteria. Further, the reason of selecting of vaccinating secondary cases ignoring the primary cases is against the collecting sample criteria in the first and third or fourth. In current study revised the 130 laboratory tests to provide the vaccine efficacy due to the restricted criteria of Jezek et al [24] eliminating the rest contacts of vaccinated and unvaccinated which are free from contact historically and clinically. Jezek et al [24] stated that the unvaccinated cases has 13.9 attack rate of younger than five years and 12.4% attack rate for younger than five years who is under 15 years. Based on the same data, the infection of

unvaccinated household in different age younger than 15 are almost same beside the attack rate of older than 15 years is zero indicating insignificant of vaccination. Therefore, the laboratory investigation of cases must be accurate number to be in calculation of vaccine efficacy. The laboratory test for vaccination and non-vaccination are 110 and 449 is excluding the query of contact of both groups and including of the two-consecutive samples craters (primary and secondary cases). However, the fourteen positive cases unconsidered cases due to negative history or clinical features as well as the remaining of contacts considered them as missing data. Conversely, Jezek et al [24] considered both which are against the selection sample criteria used in method. In current study, the household Vaccine efficacy is calculated as the result of [(50/198) – (15/71)]/(50/198)}x100=[(0.2525252525252525-0.21126760563380280/0.2525252525252525] x100 whereas the total Vaccine efficacy is calculated as a result of [(74/449)–(18/110)]/ (74/449)} x 100 = [(0.1648106904231626 - 0.1636363636363636 / 0.2837837837837838] x 100. Therefore, the household Vaccine efficacy is 16.3% whereas total Vaccine efficacy is 0.6%. The effective of vaccine in Household is more accurate due to the same exposure risk whereas the total did not have the same risk for all cases.

However, the severity of clinical presentation in unvaccinated and vaccinated people found to be 74% and 39.5% [13]. This a clear evidence of vaccine is effective in decrease the incidence severity of progress in development of acute respiratory distress syndrome, bronchopneumonia, pneumonitis and encephalitis [13] in 24.5% comparing to unvaccinated group. The severity of clinical presentations are variable may include consequences systematically such as respiratory system (acute respiratory distress syndrome, bronchopneumonia, pneumonitis), nervous system (Encephalitis, ocular infection e.g. keratitis and blindness), gastrointestinal system (diarrhea and vomiting reaching to dehydration) [13]. Kabuga and Zowalaty [25] estimate the monkeypox mortality rate between zero to ten percent whereas World health organization estimate the monkeypox mortality rate between 3 and 6%. In current research study, the mortality rate ranges from 2.7 to 10.1% when it estimated mortality rate of confirmed cases of monkeypox in 4.4% globally (Table 1). The Mortality is higher in children, young adults, and immunocompromised individuals based on world health organization. The mortality rate can be decreases as the vaccine intake increases. Yearly, the incidence of rate of monkeypox is 63 person per million in the Bumba [22] where as it raises to 553 person per million in Democratic Republic Congo [26] due to insufficient vaccination.

Conclusion

The validity of vaccine efficacy depends on several factors are the case definition should be standardized and practical consistently as well as the vaccine date well identified and infection exposure were equal in vaccinated and unvaccinated groups. Further, sex, age and race are other factors that may modified from area to other area that effect the result of vaccine efficacy. Coexistence of condition or diseases such as malnutrition or diabetes may also become other factors must considered clinically rather than statistically. Several preventive measurement such as avoid face-to-face exposure using personal protective equipment (Using mask, face shield, disposable gloves google. Etc.). The contact divided into direct physical contact such as sexual contact including multiple contact partner and condomless sexual contacts or indirect contaminated materials such as clothing or bedding. Avoid gathering place and put triage point to infected cases and contacts across. Healthcare workers must adhere to precautions including hand hygiene and use personal protective equipment (PPE) such as gloves, face mask, gown, and goggles. Further, suspected and confirmed cases should not donate blood, cells, tissue, organs, breast milk, or semen. Avoid travel cross country and get smallpox vaccination. Scientist and clinician reported any monkey case is also preventive measurement to control outbreak. Further breast-feeding should be discontinue preventing transmission from mother to child or the other way around. It is a clear message passing to entire scientist to find urgent monkeypox vaccine rather than depending on small pox vaccine effectiveness. It alerts scientist and clinician to prepare their self for endemic, epidemic or pandemic disease may occur due to lacking effectiveness vaccine and treatment.

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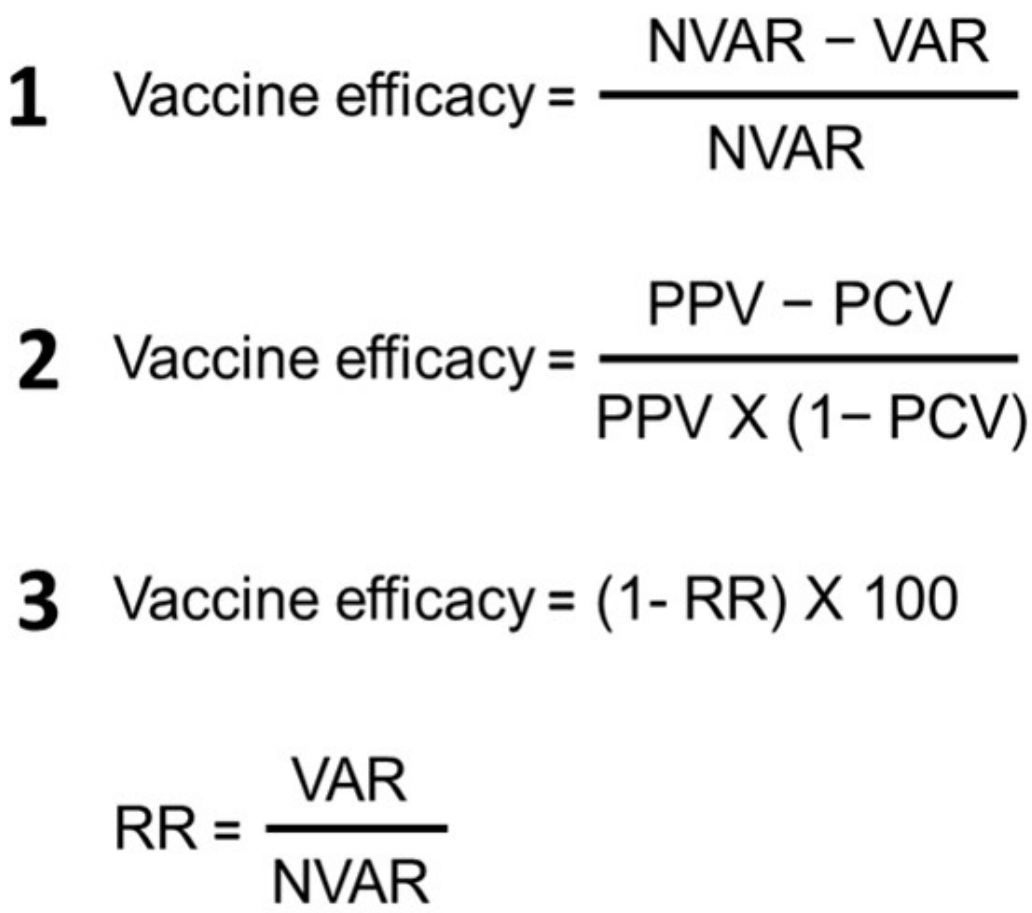

Figure 1: Vaccine Efficacy estimation methods. VAR: Attack Rate of Vaccinated, NVAR: Attack Rate of Unvaccinated, PPV: Percentage of Population Vaccinated, PCV: Percentage OF Cases Vaccinated, RR: Relative risk

Table 1: Monkeypox mortality rate are variable in different countries.

Country	Suspected Cases	Confirmed	Death	Rate %
Cameron*	25	3	2	8
Central African Republic (CAR)*	6	6	2	33.3

Democratic Republic of the Congo (DRC)* 2020	6 216	222	-***	3.6
Democratic Republic of the Congo (DRC)* 2021	3 091	83	-***	2.7
Democratic Republic of the Congo (DRC)* 2022	1 152	1 152	55	4.7
Democratic Republic of the Congo (DRC)*	138	-***	14***	10.1
Nigeria 2021	98	34	0	0
Nigeria 2022	13	4	0	0
Nigeria**	241	241	8	3.3
Total		1504	81	
The correct global mortality rate of confirmed cases	10980	1504	67	4.4%

*European Centre for Disease Prevention and Control. Monkeypox multi-country outbreak [4].
**World Health Organization - Regional Office for Africa (WHO/AFRO) [26].
Nigeria Centre For Disease Control (NCDC) [27].
*** Note: to in case of the study has no resources of confirmed cases and death, the number is corrected value due to exclusion data.