Original Article

# Comparison of pre-COVID-19 pandemic, lockdown, and postlockdown participant adherence in a phase IV clinical trial for the treatment of postexposure rabies prophylaxis

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## Abstract

**Context:** One of the most frequent difficulties encountered in clinical trials is the failure to retain participants and this is doubly important when the disease is 100% fatal. Studies conducted during the COVID-19 pandemic regarding adherence have been equivocal.

**Aims:** The aim of this study is to compare participant adherence in a phase IV clinical trial for postexposure rabies prophylaxis before the pandemic, during lockdown, and after lockdown.

**Settings and Design:** An observational study (audit).

**Subjects and Methods:** The study in May 2023 covers the period from October 2019 to March 2022. Individual participant files of recruited participants were examined for adherence to treatment in the prepandemic period, during lockdown, and postlockdown eras.

**Statistical Analysis Used:** The primary outcome measure-participant adherence anti-rabies vaccination (ARV completion) in the three timelines was compared using the Chi-squared test. The secondary outcome measures: reasons for nonadherence and potential factors associated with it done by univariate followed by multivariate logistic regression. All analyses conducted at a 5% significance level.

**Results:** A total of 455 (2046 ARV visits) participants were recruited in the original Phase IV study, with a mean (±standard deviation) age of 31.9 ± 16.23 years. The COVID-19 lockdown reported the highest nonadherence to ARV (5/26, 19%) due to travel restriction and fear of contracting SARS-CoV2 infection compared to prepandemic (9/144, 6%) and postlockdown (6/285, 2%) periods.

**Conclusion:** There was a significant reduction in participant adherence for ARV completion during the lockdown compared to the prepandemic and postlockdown timelines. Decentralized Clinical Trials may offer potential solutions to improve adherence in the context of epidemics and pandemics.

**Keywords:** Anti-rabies vaccination, compliance, pandemic, SARS-CoV2

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## INTRODUCTION

Rabies is a zoonotic disease with 100% fatality with 59,000 deaths worldwide annually that occur largely in Asia and Africa. Twenty thousand of these deaths[1,2] are in India alone.[3] Vaccination remains the most effective method for preventing rabies. Unfortunately, vaccination alone

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does not provide complete protection after high risk World Health Organization Category III exposure.[4-6] Optimal postexposure prophylaxis of Category III exposures includes proper wound care, anti-rabies vaccination (ARV), and administration (into the wound) of rabies immune globulin/antirabies monoclonal antibody for individuals who have not been previously vaccinated.

Serum Institute of India Pvt Ltd (SIIPL) developed an anti-rabies monoclonal antibody (Rabishield™) which received manufacturing and marketing authorization in India in 2016.[7] Our institute (a tertiary referral center) was the part of their multicentric phase IV clinical trial where patients with animal bites were recruited for this trial from October 2019 onwards. The trial was halted mid-way due to the COVID-19 pandemic in March 2020[8] and we restarted the trial in June 2020.

One of the most frequent difficulties encountered in clinical trials is the failure to retain participants and this is doubly important when the disease is 100% fatal.[9] Studies conducted during the COVID-19 pandemic regarding adherence have been equivocal.[10-12] Hence, an analysis of recruitment and retention of participants before the onset of pandemic, during lockdown (in India), and postlockdown would yield useful insights on participant behavior, investigator challenges, and potentially inform policy for future. This study was thus envisaged with the primary objective of comparing the participant adherence (ARV completion) in prepandemic, lockdown, and postlockdown timelines in the above trial. The secondary objectives were to assess the influence of demographics on participant adherence and to assess the reasons of nonadherence.

## SUBJECTS AND METHODS

### Ethics

The Institutional Ethics Committee approved this study (EC/OA-52/2023) and accorded a consent waiver as it was a retrospective audit. This audit was prospectively registered with the Clinical Trials Registry of India (CTRI/2023/04/051763). We also obtained the permission from the sponsor of the original regulatory trial (SIIPL, Pune) to conduct this study.

### A brief overview of the original study (as planned before the COVID-19 pandemic)

The original regulatory phase IV study (CTRI/2019/06/019622) was a multicentric randomized, parallel, active controlled trial with allocation ratio as 1:3 for Equine rabies immunoglobulin (ERIG) versus Rabishield™ (monoclonal antibody) to assess safety and immunogenicity following postexposure prophylaxis. The overall study sample was 4000 patients enrolling patients with Category III bites. The vaccination (1:1) was further divided into intramuscular (IM) versus intradermal (ID) route of administration for the ARV (Rabivax-S™).

There was total seven "site visits" for each participant, of which first visit was for administration of Rabishield™ or ERIG along with the first dose of ARV (day 0) followed by four visits, (days 3, 7, 14, and 28). The day 14 visit was applicable only for IM route (not for ID route). These were followed by visit 6 (Day 210 ± 14) and 7 (Day 365 ± 30) for the long-term safety as well as efficacy in terms of survival and immunogenicity. Each participant in the study was thus followed up for 1 year.

### Original study recruitment and duration, present study duration, timelines, and eligibility criteria

The participant recruitment started in the original study was from October 2019 to March 2022 and the last participant's last follow-up visit at our site (for ARV administration) was April 26, 2022. For the present study, we considered only the visits of ARV administration and not the safety follow-up visits as the completion of full course of vaccination is linked to survival.

We divided ARV adherence into three timelines to allow for a more meaningful comparison a prepandemic phase (October 4, 2019–March 21, 2020); and the "during pandemic" timeline was further divided into two different timelines - a lockdown phase (March 22, 2020–June 25, 2020) and a postlockdown (June 26, 2020–April 26, 2022) phase. All participants in the original study whose ARV follow-ups fell into the prepandemic or lockdown or postlockdown periods formed the inclusions for the study.

### Study procedure and information captured

We analyzed the individual participants' files to ascertain number of ARV visits completed during the three timelines. The participant information was gleaned from informed consent document and follow-up information from the source notes and the case record form. Additional information collated was demographics (age, biological sex, educational status, occupation, and residence) and animal bite-related characteristics (animal, pet/stray, provoked/unprovoked, site of wound, single or multiple wounds, nature of bite-transdermal, and scratch). Furthermore, for those who withdrew from the study, reasons were noted where possible.

### Outcome measures

The primary outcome measures were the number of participants who completed the ARV and/or the number

of missed ARV doses in the three time periods. The secondary outcome measures were the reasons for not completing vaccination; demographics, animal bite history, and vaccination completion status.

### Sample size

The sample size allocated to our site was $n = 600$, of which, we had recruited $n = 455$ participants from October 2019 to March 2022 which formed our study sample. We decided to form three subgroups from this $n_1$ (prepandemic, sample size 144/455), $n_2$ (lockdown sample size 26/455) and $n_3$ (sample size 285/455).

### Statistical analysis

Both descriptive and inferential statistics were applied. Quantitative data were expressed as mean standard deviation (SD) and categorical data as frequency (percentage) and 95% confidence intervals (CI) were calculated. Normality was assessed using the Shapiro–Wilk test. The comparison between the three timelines was done using the Chi-squared test. Logistic regression was used in both univariate and multivariate analyses. The "dependent variable" was the number of participants who completed ARV while the "independent variables" were demographics and animal bite-related characteristics. Only those risk factors with a $P < 0.2$ were subjected to the multivariate analysis. All statistical analyses were done using the Statistical Package for the Social Sciences (SPSS) software version 25, IBM Corporation, Armonk, New York and the statistical significance was set at < 0.05.

## RESULTS

### Demographic data

The mean (SD) age (years) of the 455 participants was 31.9 ± 16.23. There were 346/455 (76%) males and 109/455 (24%) females. A total of $n = 351/455$ (77%) were adults. Majority of animal bites, $n = 390/455$ (85%) were from dogs, predominantly stray $n = 352/455$ (77%), largely unprovoked $n = 334/455$ (73%), and lower extremity bites $n = 331/455$ (73%).

### Comparison of participant demographics across three timelines

Depending on the route of administration, a total of $n = 2046$ visits were required for ARV completion in all $n = 455$ participants during the entire study period. In the prepandemic, lockdown, and postlockdown phases, $n_1 = 724/2046$ (35.4%), $n_2 = 44/2046$ (2.2%), and $n_3 = 1278/2046$ (62.4%) ARV visits were scheduled. Significant differences in the number of completed visits were observed during the three timelines, as shown in Table 1. ARV completion significantly ($\chi^2$ [2, $n = 2046$] = 28.61, $P = 0.0001$) decreased during the lockdown phase (39/44, 89%) compared to pre (704/724, 97%) and postpandemic phases (1264/1278, 99%). Similarly, in the prepandemic, lockdown, and postlockdown phases, $n_1 = 144/455$ (31.6%), $n_2 = 26/455$ (5.7%), and $n_3 = 285/455$ (62.6%) participants were due for vaccination. Of these, total 135/144 (94%), 21/26 (81%), and 279/285 (98%) participants completed their vaccination per schedule. A statistically significant ($\chi^2$ [2, $n = 455$] =18.35, $P = 0.0001$) decline in vaccination was seen in the lockdown period relative to prepandemic and postlockdown period, as shown in Table 2. During lockdown, there was significant rise ($\chi^2$ [2, $n = 20$] =7.404, $P = 0.025$) patients missing the last one dose of ARV as compared to the prepandemic and postlockdown period [Figure 1].

### Univariate and multivariate analysis

In univariate analysis, a statistically significant difference was found in three variables: timelines, animal type (pet versus stray), and residence in Mumbai (participants who were living in Mumbai as permanent residents compared to those who were just visiting Mumbai due to some reason and unfortunately, had dog bite during their visit period). The multivariate analysis showed a statistically significant difference between Mumbai and non-Mumbai residence ($P = 0.048$, 95% CI: 1.014–17.179].

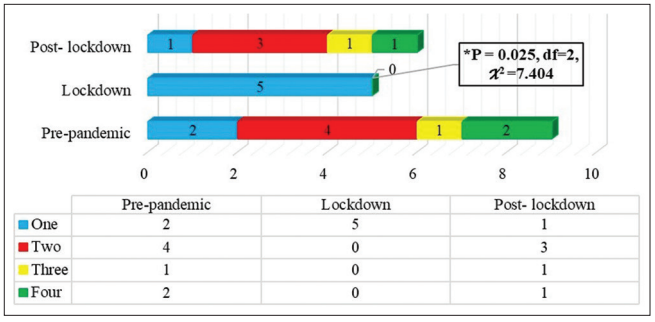



**Figure 1:** Number of Anti-rabies vaccine doses missed by the participants in the three timelines ($n = 20$). Chi squared test applied in SPSS version 25, *$P < 5\%$ is significant

**Table 1: Distribution of visits completed in the three different timelines ($n$=2046)**

| Timelines | Prepandemic, *n* (%) | Lockdown, *n* (%) | Postlockdown, *n* (%) | *P* | df | $\chi^2$ |
|---|---|---|---|---|---|---|
| Sample size | 724/2046 (35.4) | 44/2046 (2.1) | 1278/2046 (62.43) | 0.0001* | 2 | 28.61 |
| Visits completed | 704/725 (97.1) | 39/44 (88.6) | 1264/1278 (98.9) | | | |
| Visits missed | 21/725 (2.9) | 5/44 (11.4) | 14/1278 (1.1) | | | |

*$P<5\%$ is significant. Chi-squared test applied in SPSS version 25. SPSS=Statistical Package for the Social Sciences

**Table 2: Demographics of participants in the three timelines (*n*=455)**

| | Timelines | | | *P* | df | $\chi^2$ |
|---|---|---|---|---|---|---|
| | Prepandemic | Lockdown | Postlockdown | | | |
| | Timeline duration | | | | | |
| | October 4, 2019–March 21, 2020 | March 22, 2020–June 25, 2020 | June 26, 2020–April 26, 2022 | | | |
| | Number of participants having study visits in the specific timelines | | | | | |
| | $n_1$=144, *n* (%) | $n_2$=26, *n* (%) | $n_3$=285, *n* (%) | | | |
| ARV completion | | | | | | |
| Yes | 135 (93.8) | 21 (80.8) | 279 (97.9) | 0.0001* | 2 | 18.35 |
| No | 9 (6.3) | 5 (19.2) | 6 (2.1) | | | |
| Age group | | | | | | |
| Child | 22 (15.3) | 5 (19.2) | 32 (11.2) | 0.123 | 6 | 10.03 |
| Adolescent | 13 (9.0) | 2 (7.7) | 10 (3.5) | | | |
| Adult | 101 (70.1) | 18 (69.2) | 232 (81.4) | | | |
| Elderly | 8 (5.6) | 1 (3.8) | 11 (3.9) | | | |
| Gender | | | | | | |
| Male | 103 (71.5) | 20 (76.9) | 223 (78.2) | 0.304 | 2 | 2.38 |
| Female | 41 (28.5) | 6 (23.1) | 62 (21.8) | | | |
| Occupation | | | | | | |
| Service | 60 (41.7) | 8 (30.8) | 126 (44.2) | 0.576 | 8 | 6.63 |
| Student | 42 (29.2) | 8 (30.8) | 68 (23.9) | | | |
| Self employed | 18 (12.5) | 6 (23.1) | 49 (17.2) | | | |
| Homemaker | 15 (10.4) | 2 (7.7) | 19 (6.7) | | | |
| Other | 9 (6.3) | 2 (7.7) | 23 (8.1) | | | |
| Education | | | | | | |
| Illiterate and primary | 64 (44.4) | 16 (61.5) | 110 (38.6) | 0.056 | 2 | 5.78 |
| Secondary onward | 80 (55.6) | 10 (38.5) | 175 (61.4) | | | |
| Animal | | | | | | |
| Dog | 118 (81.9) | 23 (88.5) | 249 (87.4) | 0.291 | 2 | 2.47 |
| Other | 26 (18.1) | 3 (11.5) | 36 (12.6) | | | |
| Animal type | | | | | | |
| Pet | 29 (20.1) | 7 (26.9) | 67 (23.5) | 0.634 | 2 | 0.91 |
| Stray | 115 (79.9) | 19 (73.1) | 218 (76.5) | | | |
| Type of bite | | | | | | |
| Unprovoked | 107 (74.3) | 17 (65.4) | 210 (73.7) | 0.629 | 2 | 0.93 |
| Provoked | 37 (25.7) | 9 (34.6) | 75 (26.3) | | | |
| Site of bite | | | | | | |
| HFN and upper extremity | 33 (22.9) | 5 (19.2) | 86 (30.2) | 0.179 | 2 | 3.44 |
| Torso and lower extremity | 111 (77.1) | 21 (80.8) | 199 (69.8) | | | |
| Number of bites | | | | | | |
| ≤3 | 121 (84.0) | 25 (96.2) | 276 (96.8) | 0.0001* | 2 | 23.83 |
| >3 | 23 (16.0) | 1 (3.8) | 9 (3.2) | | | |
| Residence in Mumbai | | | | | | |
| Yes | 135 (93.8) | 25 (96.2) | 281 (98.6) | 0.022* | 2 | 7.59 |
| No | 9 (6.3) | 1 (3.8) | 4 (1.4) | | | |
| Investigational product | | | | | | |
| mAb | 111 (77.1) | 18 (69.2) | 198 (69.5) | 0.242 | 2 | 2.83 |
| ERIG | 33 (22.9) | 8 (30.8) | 87 (30.5) | | | |
| Route of administration | | | | | | |
| ID | 69 (47.9) | 13 (50.0) | 147 (51.6) | 0.773 | 2 | 0.51 |
| IM | 75 (52.1) | 13 (50.0) | 138 (48.4) | | | |

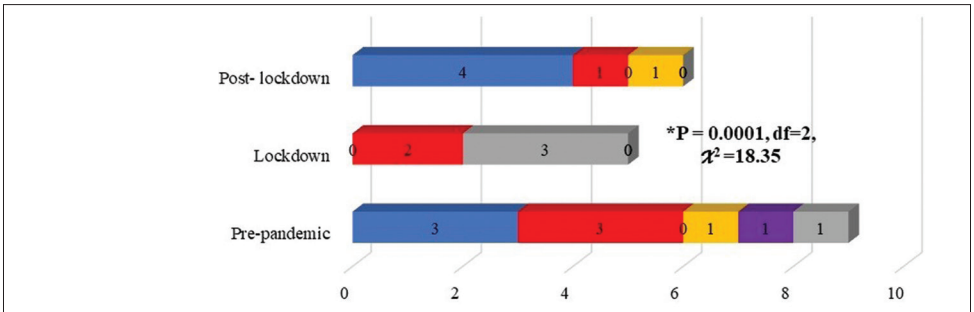
*$P<5\%$ is significant. Chi-squared test applied in SPSS version 25. SPSS=Statistical Package for the Social Sciences, ARV=Anti-rabies vaccination, ERIG=Equine rabies immunoglobulin, mAb=Monoclonal antibody, IM=Intramuscular, ID=Intradermal, HFN=Head, face and neck

### Reasons for not completing the anti-rabies vaccination

During the entire study period, a total of $n = 20$ participants did not complete their vaccination. Of these, the most common reason was migration out of Mumbai ($n = 8/20$, 40%), followed by lost to follow up ($n = 5/20$, 25%) [Figure 2]. In the prepandemic, lockdown, and postlockdown phases, $n_1 = 9/144$ (6.3%), $n_2 = 5/26$ (19.2%), and $n_3 = 6/285$ (2.1%) participants not completed the vaccination which was statistically significant ($\chi^2$ [2, $n = 455$] =18.35, $P = 0.0001$). The detailed reasons are depicted in Figure 2.

## DISCUSSION

In the present audit, we found that the period of COVID-19 lockdown reported highest nonadherence to ARV (5/26, 19%) due to travel restriction and fear of contracting SARS-CoV2 infection relative to prepandemic (9/144, 6%)




| | Pre-pandemic | Lockdown | Post- lockdown |
|---|---|---|---|
| Migration from study site | 3 | 0 | 4 |
| Lost to follow up | 3 | 2 | 1 |
| Protocol violation due to lockdown | 0 | 3 | 0 |
| Consent withdrawal | 1 | 0 | 1 |
| Local or systemic toxicity | 1 | 0 | 0 |
| ERIG hypersensitivity | 1 | 0 | 0 |

**Figure 2:** Reasons for not completing Anti-rabies vaccination during the three timelines ($n$ = 20). Chi squared test applied in SPSS version 25, *$P$ < 5% is significant

and postlockdown (6/285, 2%) periods and patients took their doses locally. Two participants skipped their last dose of ARV as they lacked the financial resources to travel to the institute for vaccination.

In this study, the age of the patients was similar to previous studies.[13,14] Males were predominant, reflecting findings in other studies,[14,15] possibly indicating their proactive health-seeking behavior. Male dominance also highlights the common underrepresentation of women in clinical trials.[16-18] The study focused on animal bites, with 85% involving dogs and 73% occurring on lower extremities aligning with the findings from previous studies.[14,15,19,20] During the COVID-19 pandemic, there was a shift, with 23% reporting bites from pet animals versus only 7% reported in a previous study conducted by Sahu *et al*.,[14] reflection a selection bias due to reduced exposure to stray dogs due to lockdown and traveling difficulties.

The significant reduction in the participant adherence for ARV completion during the lockdown as compared to the prepandemic and postlockdown timelines (81 vs. 94 and 98%) was probably primarily due to travel restriction and initial fear of contracting the SARS-CoV2 infection. A study conducted by Pal *et al*. in 2021[10] to determine adherence to ARV in patients with animal bites who presented to the emergency department during the COVID-19 pandemic showed that lack of adherence to ARV was seen in almost a quarter ($n$ = 32; 26.2%) of patients of which forgotten dates ($n$ = 11; 34.4%) was the most common cause. Another study conducted by Nadal *et al*.[11] reported that adherence to postexposure prophylaxis decreased due to fear of contracting COVID-19 infection and difficulties in reaching healthcare centers during the pandemic. Conversely, Mohammad Basir *et al*.[12] reported that the rabies postexposure vaccination was not affected by the pandemic COVID-19.

As per the data in public domain,[21] the deaths due to rabies (notifiable disease in India) were 78 (2019), 35 (2020), 56 (2021), and 51 (2022). Decentralized clinical trials (DCTs) can be a potential solution for improving adherence in pandemics, especially for a disease such as rabies. Measures such as participants taking the vaccination locally become crucial. DCTs also termed "direct-to-participant trials" or "virtual" studies[22] and are the clinical trials in which the prerequisite for patients to physically access hospital-based trial sites is reduced or eliminated. DCTs can include the direct delivery of investigational products to participating subjects, laboratory examinations, and/or instrumental tests carried out in centers other than the trial site and close to the patient's home and home visits by healthcare professionals.[23] In the original regulatory study, three participants received the ARV at a local hospital during the lockdown, which led to their withdrawal from the study as per the original protocol. However, the implementation of DCT was possible in this scenario-as the ARV used in the trial is a marketed product and the same brand of ARV could have been given to the participants at the nearby clinics and they could have been retained in the trial. Whenever IP administration is not necessary, Digital Health Technologies can be employed (for example only data capture).[24]

The COVID-19 pandemic not only affected the participant adherence due to travel restrictions but the overall recruitment was also impaired which is line with other studies.[25,26] In the present study, only 6% of the total participants had study visits during the lockdown period.

This was due to the fact that the recruitment of new participants was completely and immediately halted after the declaration of the lockdown. Few participants who were recruited during the last 28 days before declaration of lockdown were had their study visits for the ARV completion.

In addition, the COVID-19 pandemic not only affected the researchers but also non-Mumbai-based participants who returned to their native places during the pandemic, due to unemployment and lacking financial resources. Thus, the permanent residence in Mumbai was found the only significant factor affecting ARV completion.

Despite the travel restrictions and initial SARS-CoV-2 fears, ARV completion rates remained higher than in nonpandemic outpatient/emergency department-based studies (ranging 43%–68%)[13-15,27-30] and can be attributed to telephonic reminders, detailed counseling, travel reimbursement, shorter waiting times, and flexible visit timings as well as the Hawthorne effect.[31]

The strengths of our study lie in the three periods comparison, before pandemic, lockdown, and after lockdown. As the data were obtained from a regulatory study the quality of data and documents was high; hence, there was no missing data or misclassification seen despite being a retrospective audit. However, it is limited by the low to follow up numbers during the lockdown, the study being restricted to a single center, thus lacking generalizability. Lack of association between ARV completion and independent variables is likely due to variable sample sizes in three timelines and considerable homogeneity in the data.

In summary, there was a decline in ARV completion during lockdown compared to prepandemic and postlockdown period. Despite travel restrictions and the fear of catching the SARS-CoV-2 infection, the percentage of ARV completion during the lockdown is still higher than the previous studies. Exploring DCTs during pandemics, especially for diseases with a 100% case fatality, is the way forward for preparedness for any future pandemic.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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