# *Synergistic Effect of NMV-r and Acquired Immunity in Reducing Severe COVID-19*

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Weihang Bao[1], Wayne Wisemandle[2], Heidi Leister-Tebbe[3], Romina Quercia[4], Jennifer Hammond [3]
[1]Pfizer, Inc., New York, NY, USA, [2]Pfizer Inc., Lake Forest, IL, USA [3]Pfizer Inc., Collegeville, PA, USA, [4]Pfizer Inc., London, UK

## BACKGROUND AND OBJECTIVE

Both immunity and nirmatrelvir-ritonavir treatment (**NMV-r**) are known to lower the risk of **severe COVID-19** including hospitalization or death. Here we assessed if the protective effects of NMV-r and acquired **immunity** (via vaccination or prior viral exposure indicated as serologic positivity) were synergistic and, if so, to evaluate the strength of that synergy.

## METHODS

Non-hospitalized symptomatic adults infected with COVID-19 were enrolled into two similarly designed double-blind clinical trials, EPIC-HR JHammond 2022, 2024 and EPIC-SR JHammond 2024, and randomized (1:1) to receive NMV-r or placebo for 5 days. The IPTW (Inverse Probability Weighting for Treatment) was used to adjust for baseline imbalance between patients with and without immunity. All participants with risk factors for severe COVID-19 in the two published trials were included to evaluate synergy between NMV-r and acquired immunity, with synergy assessed as Excess Absolute Risk due to Interaction (**EARI>0**), Relative Excess Risk due to Interaction (**RERI**>0) and Attributable Proportion (**AP**>0) MJKnol2011, TJVanderWelee 2014. A Generalized Estimating Equation model was used to analyze proportion of patients with severe symptoms.

## RESULTS

- Among the 2572 patients, baseline characteristics were well balanced between treatment groups, but not necessarily between patients with or without immunity (Table 1).
- SAR-CoV-2 concentration was lower among patients with immunity on Day 1, and was reduced significantly more at Day 5 with NMV-r.
- Relative to patients with no immunity and treated with placebo, the risk of hospitalization due to COVID-19 or death was reduced (95% CI) by 83% (71-90%) with acquired immunity alone, 85% (69-93%) with NMV-r alone, and 96% (88-98%) with both together. After adjusting for imbalance in baseline characteristics using Inverse Probability Weighting for Treatment, the respective risk reductions were 81.3%, 85.7% and 94.7%.

**Table 1. Baseline Characteristics and SAR CoV-2 Concentration**

| | Placebo/ No Immunity | Placebo/ Immunity | NMV-r/ No Immunity | NMV-r/ Immunity |
|---|---|---|---|---|
| Baseline Characteristics | | | | |
| #Patients, N | 497 | 793 | 475 | 807 |
| Age (Yrs), Mean (SD) | 46.2 (16.3) | 45.4 (14.4) | 44.9 (16.0) | 45.3 (14.5) |
| Female, n (%) | 249 (50.1) | 387 (48.8) | 236 (49.7) | 405 (50.2) |
| Race White*, n (%) | 389 (78.3) | 546 (68.9) | 361 (76.0) | 553 (69.0) |
| US region*, n (%) | 123 (24.8) | 360 (45.4) | 123 (25.9) | 355 (43.4) |
| ≥2 Risk Factors* | 310 (62.4) | 424 (53.5) | 270 (56.8) | 436 (54.0) |
| Completed Vaccination, n (%) | 0 (0) | 314 (39.4) | 0 (0) | 317 (39.3) |
| SARS CoV-2 Concentration, $log_{10}$ copies/mL | | | | |
| Detectable at Day 1 | 444 | 589 | 436 | 581 |
| Day 1 Mean (SD)* | 6.5 (1.6) | 5.1 (2.2) | 6.5 (1.6) | 5.4 (2.2) |
| Day 5 Mean (SD) | 4.3 (2.1) | 2.7 (2.1) | 3.3 (1.7) | 2.2 (1.8) |
| Change (SD)** | -2.2 (1.7) | -2.4 (1.8) | -3.2 (1.6) | -3.2 (1.8) |

* P-value < 0.05 for the comparison between patients with vs without **immunity** (vaccinated or sero+).
** P-value < 0.05 for the comparison between NMV-r vs placebo.

**Figure 1. The protective effects of NMV-r and acquired immunity on severe COVID-19 were synergistic, shown as a 22.7-fold increased risk in the absence of protection, with 72.6% of the increase, or 16.5-fold, attributed to the synergy**

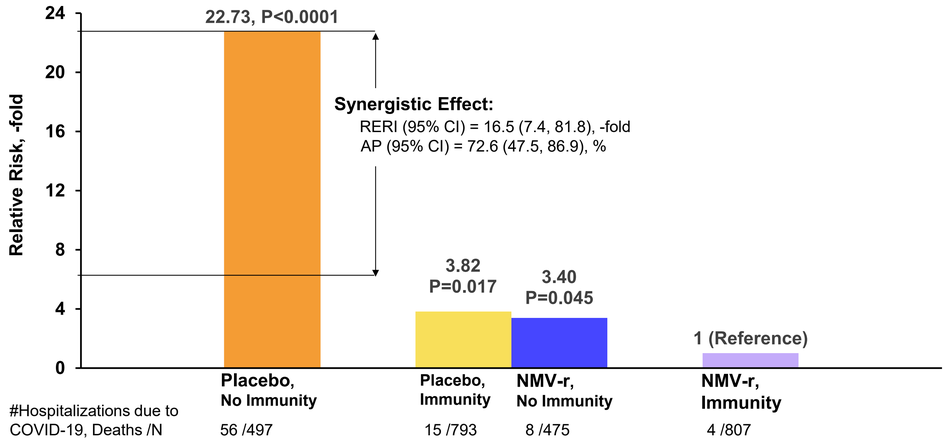


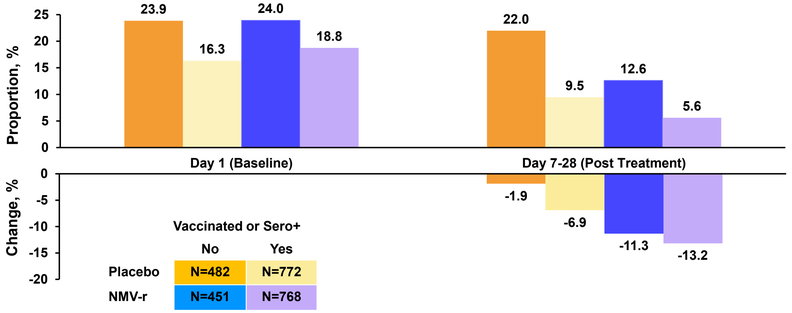

**Table 2. Synergy Reflected in Assessing #Patients Who Had Medical Visits, or Severe COVID-19 Symptoms**

| | Placebo/ No Immunity | Placebo/ Immunity | NMV-r/ No Immunity | NMV-r/ Immunity | Level of Synergy (95% CI) |
|---|---|---|---|---|---|
| **N** | 497 | 793 | 475 | 807 | |
| **COVID-related Hospitalization or Death, n (%)** | 56 (11.27) | 15 (1.89) | 8 (1.68) | 4 (0.50) | |
| Death, **n (%)** | 11 (2.21) | 2 (0.25) | 0 | 0 | |
| Absolute Risk Increase, %<br>P-value | 10.8<br><0.0001 | 1.4<br>0.010 | 1.2<br>0.063 | Reference | EARI* in % = 8.2 (5.0, 11.4) |
| Relative Risk Increase, -fold<br>P-value | 22.7<br><0.0001 | 3.8<br>0.017 | 3.4<br>0.045 | Reference | RERI in fold = 16.5 (7.4, 81.8)<br>AP in % = 72.6 (47.5, 86.9) |
| **Medical visits, n (%)** | 67 (13.48) | 32 (4.04) | 14 (2.95) | 14 (1.73) | |
| Absolute Risk Increase, %<br>P-value | 10.8<br>< 0.0001 | 2.3<br>0.0060 | 1.2<br>0.18 | Reference | EARI in % = 8.2 (4.5, 12.0) |
| Relative Risk Increase, -fold<br>P-value | 7.8<br><0.0001 | 2.3<br>0.0076 | 1.7<br>0.16 | Reference | RERI in fold = 4.7 (2.5, 10.0)<br>AP in % = 61.3 (39.4, 78.4) |
| **Severe COVID-19 Symptoms** | | | | | |
| Change from Day 1 to 7-28, % of patients | -1.9 | -6.9 | -11.3 | -13.2 | |
| Absolute Risk Increase, % of patients<br>P-value | 16.4<br><0.0001 | 3.9<br>0.0040 | 7.0<br><0.0001 | Reference | EARI in % = 5.5 (0.02, 11.0) |
| Relative Risk Increase, -fold<br>P-value | 3.1<br><0.0001 | 1.9<br>0.0005 | 1.8<br>0.0045 | Reference | RERI in % = 38 (-33, 104)<br>AP in % = 12.3 (-0.11, 0.32) |

**Medical Visits** included hospitalization, emergency room, practitioner's office, home healthcare services, urgent care, telephone consultation, outpatient infusion center, etc
***EARI** = Excess Absolute Risk due to Interaction, effect of combined NMV-r and immunity – effect of NVM-r – effect of immunity, e.g. 8.2 = 10.8 - 1.4 - 1.2

- The synergistic effect was consistently observed in males (RERI=19.1-fold, AP=71.4%), females (14.0-fold, AP=79.0%), with immunity by vaccination (RERI=8.8, AP=73.6%), and with immunity/sero+ without vaccination (RERI=39.8, AP=72.1).

**Figure 2. Proportion of Patients with Severe COVID-19 Symptoms following treatment during Day 7-28 was reduced by 37.1% with immunity alone, 42.7% with NMV-r alone, and 67.6% with both**




**Symptoms** included cough, shortness of breath or difficulty breathing, fever, chills or shivering, muscle or body aches, diarrhea, nausea, vomiting, headache, sore throat, stuffy nose. Patients being hospitalized for COVID or died were considered to have severe symptoms.

## CONCLUSIONS

- Among patients at high risk to develop severe COVID-19, NMV-r and acquired immunity provided incremental, synergistic protections against severe COVID-19.
  - With both protections, the rate of severe COVID was lowered to 0.5% among infected high-risk patients in the middle of the Pandemic.
  - With no protection the risk of severe COVID-19 was 11.27%, a more than 20-fold deleterious increase.
  - Two protections were significantly better than one, preventing a greater than 3-fold relative risk associated with missing either.
- The synergistic protective benefit was also reflected in the severe symptoms and the number of medical visits or consultations related to COVID-19.

## Generalizability/Applicability of Findings

- The low rate of severe COVID-19 in the presence of both immunity and NMV-r explains the decreasing rate of hospitalizations and deaths during the endemic phase of COVID-19. The rate of severe disease is kept low as effective therapeutics emerge, and population-wide immunity increases due to vaccination and viral exposure.
- In the absence of immunity and effective therapy, high rates of severe disease should be anticipated in future epidemics or pandemics.