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## **Effect of Ivermectin Mass Drug Administration on the COVID-19 Pandemic: An Ecological Study with Special Reference to the STATE of Uttarakhand, India**

**Nidhi Uniyal**

Associate Professor, Department of Medicine, Government Doon Medical College, Dehradun, HNB Medical Education University, Uttarakhand, India

**Hem Chandra Pandey**

Vice Chancellor, HNB Medical Education University, Uttarakhand, India

**Ashutosh Sayana**

Government Doon Medical College, Dehradun, HNB Medical Education University, Uttarakhand, India

**Narayan Jeet**

Professor, Department of Medicine, Government Doon Medical College, Dehradun, HNB Medical Education University Uttarakhand, India

**Anurag Agrawal**

Professor, Department of TB and Chest Medicine, Government Doon Medical College, Dehradun, HNB Medical Education University, Uttarakhand, India

**Sadhana Awasthi**

Professor, Department of Community Medicine, Shushila Tiwari Medical College, Haldwani, HNB Medical Education University, Uttarakhand, India

**Saurabh Agarwal**

Professor, Department of Medicine, SGRRIMHS, Dehradun, Uttarakhand, India

**Puneet Kumar Gupta**

Assistant Professor, ICAI Business School, The ICAI University, Dehradun, Uttarakhand, India

**Abstract**---Uttarakhand, a hilly state of India adopted the strategy of mass drug administration of ivermectin during the second wave of COVID-19 pandemic as a measure to control the peak due to failing health infrastructure and health facility with sudden cases surge. This study was hereby planned with an aim of analyzing the effect of mass drug administration of ivermectin on the COVID-19 pandemic progression in the State of Uttarakhand. The trend of pandemic progression in five states of India was studied taking case growth rate, active case rate and case fatality rate as indicators. The percentage change in the indicators with the progression of pandemic was calculated for all five states and compared. The projected increased number of deaths, the state of Uttarakhand would have experienced, if the state had the declining average case growth of the other states taken for study was also calculated. The data analysis shows that the Uttarakhand had a sharp fall in the active cases by 3 to 4 weeks post lockdown, the period corresponding with maximum coverage of ivermectin distribution in the state, compared to four other states. Uttarakhand was also able to control the rising case fatality rate in state, by early decline in case growth rate and also partly due to decrease in severity of cases, as ivermectin is hypothesized to affect disease severity if given as early treatment. The study observed that mass drug administration of ivermectin had beneficial effect on the pandemic control in the state of Uttarakhand.

**Keywords**---COVID-19, Ivermectin, mass drug administration.

## Introduction

SARS-COV-2 was declared a pandemic by WHO in march 2020 and since then it had effect globally causing large number of morbidity and mortality. Two years into pandemic and still not a single antiviral drug has stand out as an effective measure for prophylaxis against the disease. Vaccination is going around worldwide but still the countries are going through the waves of pandemic waxing and waning causing high mortality and morbidity. New strains are developing, creating doubts about the efficacy of vaccine against them. Vaccine availability is also a big problem especially in developing world.

In an attempt to contain the spread of disease along with an aim of providing an effective treatment, efforts are being done worldwide to discover new drugs. Beside this, a number of old drugs have been repurposed. Among the repurposed drugs the most controversial had been the use of ivermectin. Ivermectin is being widely used as anti-parasite drugs for past 50 years in the animals and also in human beings against the filaria and strongyloidiasis. In vitro study found to have an inhibitory action of ivermectin against the replication of the SARS-COV-2 virus (Arevalo et al., 2021; Caly et al., 2020). It is known to have anti-inflammatory and immunomodulatory action also, though the mechanism yet unknown and thus providing hypothesis for its beneficial effect in the late stages of COVID-19 illness (Zaidi & Dehgani-Mobaraki, 2021).

WHO has recommended the use of ivermectin in clinical trials only in their guidelines issued on 31<sup>st</sup> March 2021, (Therapeutics and COVID-19, Living Guideline, WHO-31st March 2021). A study by Hellwig & Maia (2021), have made an observation of a negative co-relation between the incidence of COVID-19 and prophylactic chemotherapy by ivermectin irrespective of the population covered in the mass drug administration, (Hellwig & Maia, 2021). In India, the COVID-19 treatment guidelines issued by the Ministry of Health and Family Welfare/ Indian Council of Medical Research dated 24<sup>th</sup> May have included ivermectin in their treatment protocol recommending considering ivermectin for early treatment in individuals with high risk factors (National Clinical Management Protocol COVID-19, Government of India, Ministry of Health Family Welfare, version 6, 24<sup>th</sup> May 2021). Similar recommendations have been made by the esteemed institution of AIIMS, Delhi, (AIIMS/ ICMR-COVID-19 National Task Force/ Joint Monitoring Group. Ministry of Health & Family Welfare, Government of India Clinical Guidance For Management Of Adult COVID-19 Patients 17 May 2021).

Uttarakhand, a hilly state of India adopted the policy of ivermectin mass drug administration with an objective to reduce the transmission of the disease, by decreasing the viral load in the symptomatic/asymptomatic carriers, along with an effective lockdown. This study was hereby planned with an aim of analyzing the effect of mass drug administration of ivermectin on the COVID-19 pandemic progression in the State of Uttarakhand.

## Methodology

The data pertaining to pandemic of various states for the analysis was obtained from the available internet source (<https://flevy.com/coronavirus/india>), and data for ivermectin distribution in Uttarakhand State was obtained from the Infectious Disease Surveillance and Prevalence Centre of state (Uttarakhand State Control Room Integrated Disease Surveillance Programme Directorate of Medical Health & Family Welfare, Uttarakhand, Dehradun). The indicators used for study were the case *growth rate* because it is a natural way to capture how quickly the number of infections is changing day by day. A negative growth rate indicates that the epidemic is under control. The daily growth rate ( $\mu$ ) equals to  $\Delta N$  on a given day divided by the total number of cases from the previous day ( $N$ ),  $\mu = \Delta N/N$  where  $\Delta N$  is the number of new cases detected daily. Active case rate, calculated by dividing the total number of active cases prevalent in the place by the total number of cases from the previous date. Active cases consist of number obtained after deducting the total recovered cases and total death from the total cases at a point. Total cases are the recorded cumulative positive cases at a point (defined as the date for which the data is being evaluated). Case fatality rate which was calculated by dividing the total deaths by the total number of cases at that point. Ivermectin coverage rate of a district/state is the percentage of total population covered in a district/state by drug distributing agencies at a particular time. The data was obtained for 5 states to study the pandemic trend in the states. The five states taken for analysis were Delhi, Tamil Nadu (TN), Maharashtra, Himachal Pradesh (HP) and Uttarakhand. All the states taken for study have adopted the policy of lockdown with varying strictness as the pandemic progress. Uttarakhand was the only state which took the Ivermectin Mass Drug Administration program to control the rising case growth rate of pandemic an additional measure. The

pandemic curves for five states were drawn taking the case growth rate, active case rate and the case fatality rate. The data was analysed as the percentage drop attained in the case growth rate, active case rate and the case fatality rate of various states in next 5 weeks post lockdown. The projected number of deaths for next 5 weeks period after corona curfew imposition in Uttarakhand state was also calculated in following steps. First the number of days Uttarakhand state would have taken to reach an active case rate of 5%, was calculated by applying the declining case rate of 4 states taken in study. Average daily cases in the post covid period calculated which was = [total cumulative cases on 6<sup>th</sup> June in Uttarakhand (day when the active cases rate ~5%)-total cumulative cases on 11<sup>th</sup> May (day of corona curfew imposition in state)]/ 27 days\*\*.

\*\*difference in no. of days from 6<sup>th</sup> June to 11<sup>th</sup> may.

Average case fatality rate of Uttarakhand in post corona curfew period was then applied to the daily average cases of Uttarakhand in that period and the projected death calculated.

Projected death = average daily cases\*average case fatality rate \*no of days in excess for reaching the active case rate of 5%.

## TIMELINE FOR TREND DESCRIPTION

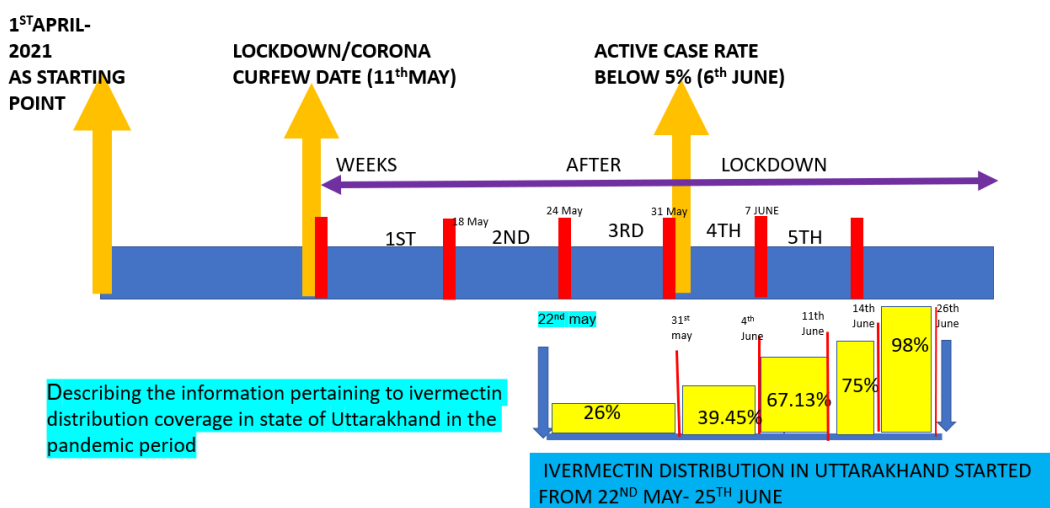


Figure 1. Distribution of Ivermectin in the state of Uttarakhand during the pandemic

Ivermectin Mass Drug administration was started in the state of Uttarakhand around 22<sup>nd</sup> may that is 11 days post lockdown initiation.

## Results

### Case Growth Rate (CGR)

Case Growth rate- 5 STATES-

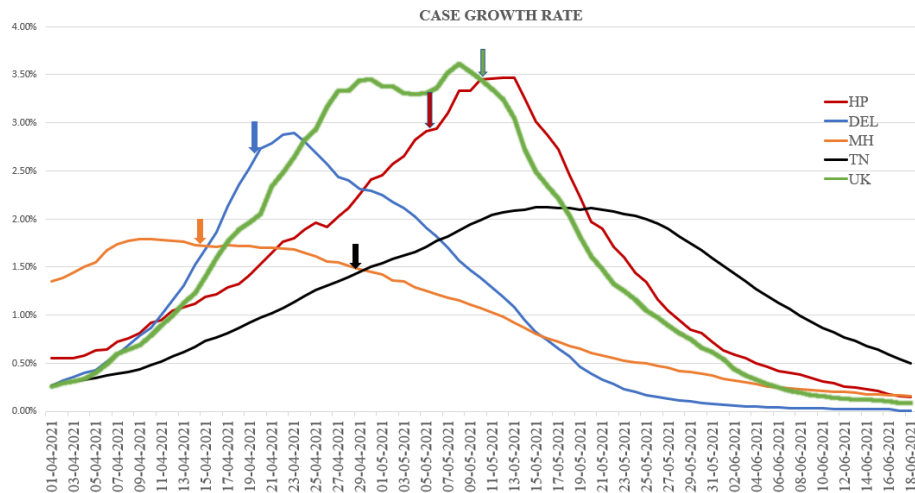


Figure 2. Curve showing case growth rate of five states of India

The arrows depicting the time of initiation of lockdown in states by the local administration.

Uttarakhand and HP observed high percentage drop in Case growth rate during the progress of lockdown

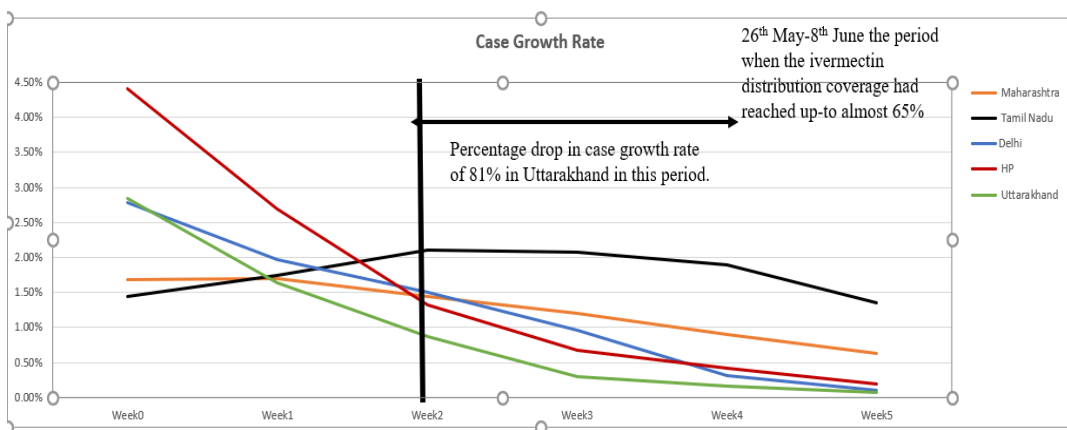


Figure 3. Curve depicting the weekly decline in case growth rate across five states of India as corona curfew progresses

Figure 3 depicts the parallel pattern of the declining rate of cases between Himachal Pradesh and Uttarakhand.

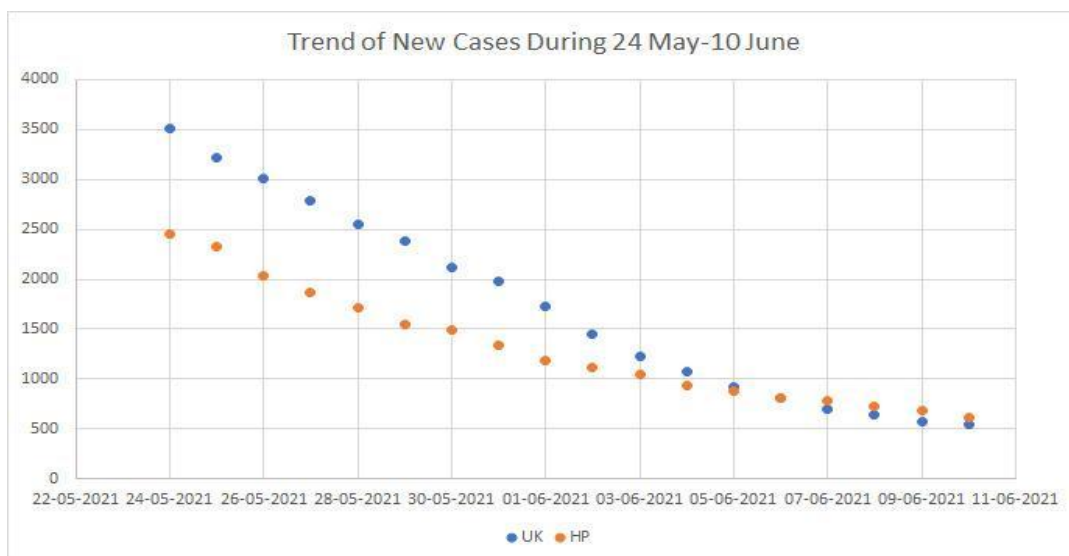


Figure 4. Curve showing new cases of Himachal Pradesh and Uttarakhand in the month of May-June

The plotted curve as shown in figure 4 showed a difference of 1000 new cases on 24<sup>th</sup> May, which decreased rapidly and by 5<sup>th</sup> June no difference in new cases was observed in between the two states of Himachal Pradesh and Uttarakhand.

Table 1

Percentage drop in case growth rate in various states of India post corona curfew imposition

Number of weeks post lockdown	Maharashtra	Tamil Nadu	Delhi	Himachal Pradesh	Uttarakhand
First 2 weeks post lockdown	14.3%	-44.8%	45.7%	69.8%	69.5%
3 <sup>rd</sup> and 4 <sup>th</sup> week post lockdown	37.5%	10.0%	78.8%	68.4%	81.6%
5 <sup>th</sup> week post lockdown	30.5%	28.6%	65.6%	54.8%	50.0%

### Active case rate

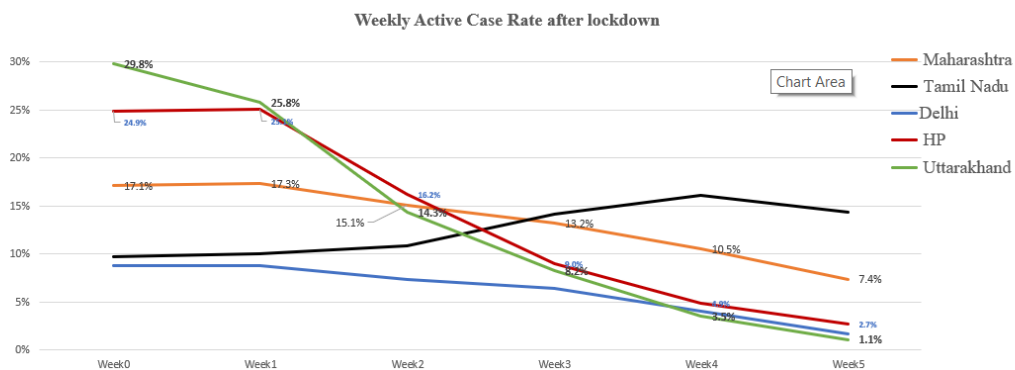


Figure 5. Weekly active case rates of various states post lockdown

Table 2  
Percentage Drop in the weekly rate of active cases of various states of India post lockdown

% Drop in ACR	Maharashtra	Tamil Nadu	Delhi	Himachal Pradesh	Uttarakhand
First 2 weeks of lock down	11.7%	-10.8%	15.7%	34.8%	51.9%
3 <sup>rd</sup> and 4 <sup>th</sup> week of lockdown	30.5%	-48.6%	45.7%	69.9%	75.5%
5th week of Lockdown	29.5%	10.4%	56.8%	44.6%	68.6%

### Case fatality rate

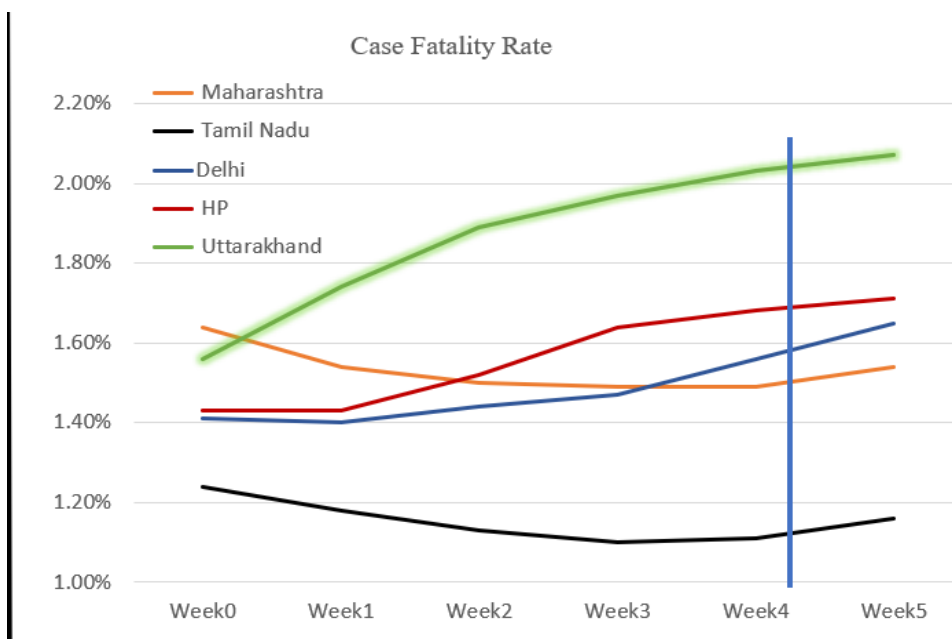


Figure 6. Case fatality curve for various states of India

Table 3

Percentage drop in the case fatality rate of various states with progression of covid curfew

% drop in Case growth rate	Maharashtra	Tamil Nadu	Delhi	HP	Uttarakhand
First 2 weeks of lock down	8.5%	8.9%	-2.1%	-6.3%	-21.2%
3 <sup>rd</sup> and 4 <sup>th</sup> week of lockdown	0.7%	1.8%	-8.3%	-10.5%	-7.4%
5th week of Lockdown	-3.4%	-4.5%	-5.8%	-1.8%	-2.0%

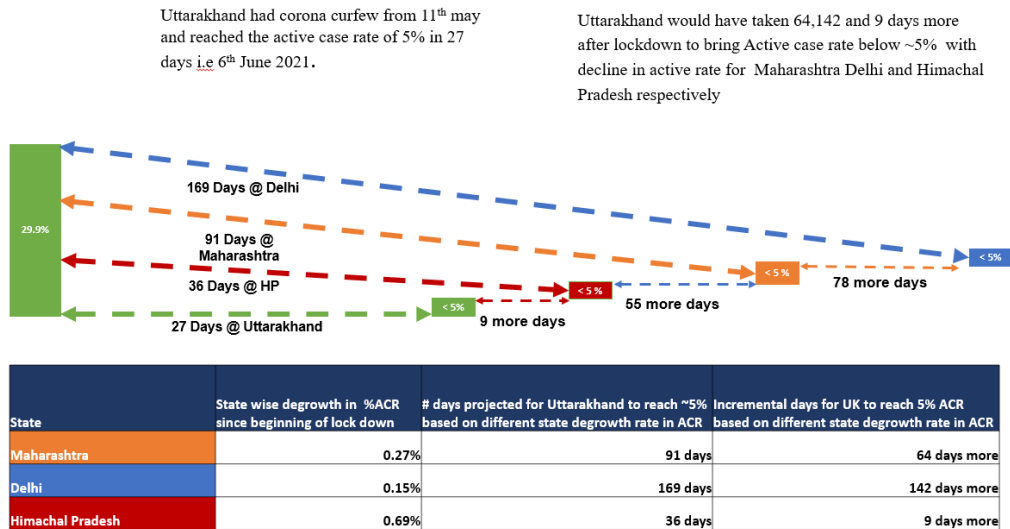
Table 3 depicting the percentage drops in the case fatality rate of the 5 states under study with progression of pandemic.

### Projected death rate

Maharashtra had an average declining rate of 0.27% per day in active case rate since the beginning of lockdown till it attained an active case rate of 5% while Delhi and Himachal Pradesh had 0.15% and 0.69% declining rate per day respectively in active cases (Figure7). Uttarakhand attained an Active Case Rate of 5% in a span of 27 days post lockdown. The average case fatality rate of state in the given period was 1.8%. If the Active Case Growth Rate of the state would have followed the declining trend of Maharashtra, Delhi and Himachal Pradesh then it



would have taken an average of 91 ,169 and 36 days post lockdown respectively to reach an active case rate of 5 % .



\*ACR – Active case rate

\*\*Note: ACR for Tamil Nadu is still above 5%

Figure 7. Projected number of days Uttarakhand would have taken to attain the active case rate of less than 5% if it had declined at similar rate as the other states under study

Table 4

Projected number of deaths Uttarakhand would have attained had its active case rate declined with that of other states under study

State	Incremental days with states decline ACR	Total Projected Incremental Deaths
Maharashtra	64	3,289
Delhi	142	7,297
Himachal Pradesh	9	463

Avg Fatality Rate =1.8%

Average Total cases per day (Uttarakhand) b/w 11<sup>th</sup> may and June 6<sup>th</sup>=2855

Total Projected Incremental Deaths =

Avg Fatality Rate \* # incremental days with states decline ACR \* Average Total cases per day (Uttarakhand) b/w 11<sup>th</sup> may and June 6<sup>th</sup>

ACR is Active Case Rate

Uttarakhand state would have additional 3,289, 7,297 and 463 death if the declining rates of Maharashtra, Delhi and Himachal Pradesh was applied respectively to the state of Uttarakhand.

### Co-Relation between ivermectin coverage in state and total positivity rate

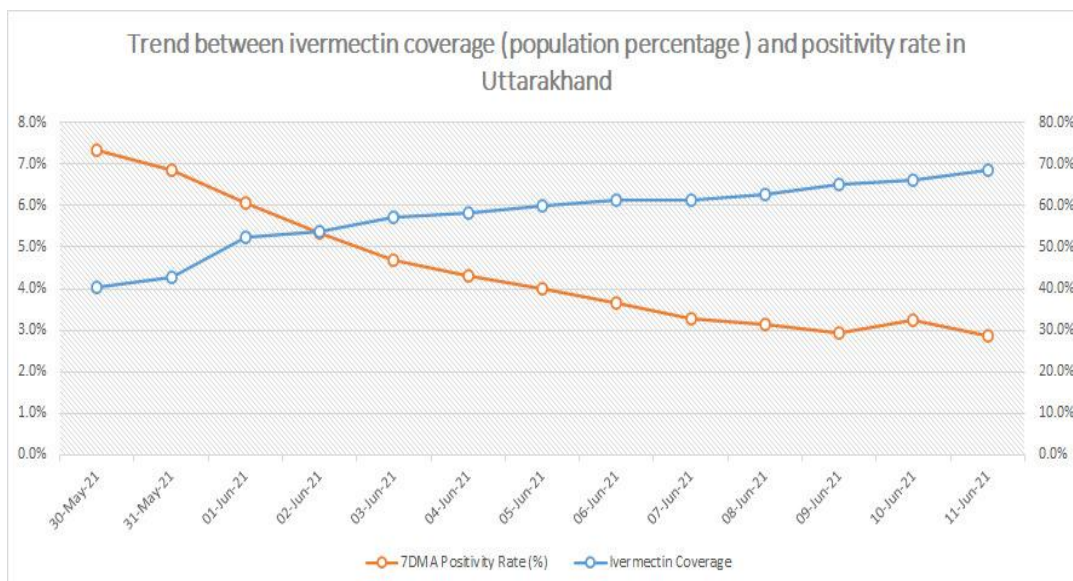


Figure 8. Co-relation between ivermectin coverage and the 7 Day Moving Average positivity rate of samples for Uttarakhand state

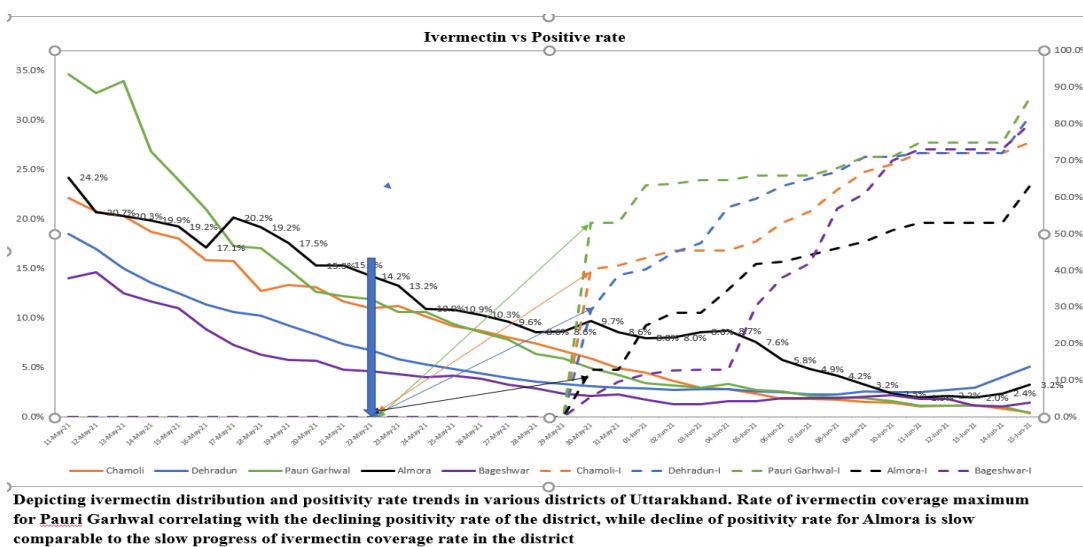


Figure 9. Trend of ivermectin distribution and positivity rate in various districts of Uttarakhand

Figure 8 and figure 9 show negative linear co-relation between the rate of ivermectin distribution coverage and the 7 day moving average of sample positivity rate. As evident from the figures the sample positivity rate decline is high for Pauri Garhwal while decline of positivity rate for Almora is low which is comparable to the progress of ivermectin coverage rate in the districts. As graph

shows linear relationship between ivermectin coverage and positivity rate, Karl Pearson Correlation Coefficient was obtained for the same and it was -0.9826 (strong indirect relationship) which is significant at 1 % level of sign (p-value=0.00002).

## Discussion

The study by Meo, S.A and et al have observed that 15 days after the lockdown, daily cases of COVID-19 and the growth factor of the disease showed a declined trend, with no significant decline in the prevalence and mortality (Meo et al., 2020). The five states taken for analysis have imposed lockdown as a measure to curb the rising cases of the covid. The state of Uttarakhand had taken an additional measure of the ivermectin Mass Drug Administration. The comparison for the percentage change within the state in the indicators was thus analysed on weekly basis post lockdown for each state.

In a study by Chaccour et al, the viral load of the covid patients did decrease by 7<sup>th</sup> day in the randomized controlled trials after single dose of ivermectin within 48 hours of the infection onset (Chaccour et al., 2021). Uttarakhand observed the maximum percentage drop in case growth rate of 81% in 3<sup>rd</sup> and 4<sup>th</sup> week of post covid curfew (Table1), which corresponds with the period of 25<sup>th</sup> May to 7<sup>th</sup> June, the period of ivermectin distribution in the state. Delhi achieved a percentage drop of 78.8% in the same periods of lockdown while Himachal Pradesh achieved 68.4%. Figure 5 and table 2 clearly depicts that the maximum percentage drop in active cases was in the state of Uttarakhand with the progression of corona curfew (51.9%, 75.5% and 68.6% respectively in 2<sup>nd</sup>, 4<sup>th</sup> and 5<sup>th</sup> weeks post lockdown for Uttarakhand) compared to all other 4 states taken for study.

Himachal Pradesh and Uttarakhand have comparable population density (123 per sq km for Himachal Pradesh and 189 per sq km for Uttarakhand), (2019-2022 population U, Research papers on Population dynamics and Social affair) and also have same geographical terrain. The case growth rate curve (figure 3 ) is also depicting the same pattern for these 2 hilly states. We thus analysed our data further for these two hilly states. Uttarakhand and Himachal Pradesh had a case growth rate (7 day moving average) of 3.53% and 3.33%. By 6<sup>th</sup> of June, CGR in Uttarakhand dropped to 0.25% and 0.42% for Himachal Pradesh respectively. This drop in case growth rate is 40.5% more for Uttarakhand compared to Himachal Pradesh. Himachal Pradesh imposed corona curfew while Uttarakhand adopted Mass Drug Administration of ivermectin along with corona curfew in same period.

Case fatality rate is second highest for Uttarakhand (2.15%). Total deaths reported for Uttarakhand till July 9, 2021 were 7,338. Uttarakhand had a gain of 21% in case fatality rate in first 2 weeks of post-lock down which was 6.3%, 2.1%, 8.9% and 8.5% for Himachal Pradesh (HP), Delhi, Tamil Nadu (TN) and Maharashtra respectively. This reduced to 7.4% in 3<sup>rd</sup> and 4<sup>th</sup> week and to 2 % in 5<sup>th</sup> week of post lockdown for Uttarakhand, while HP had a gain of 10.3% in 3<sup>rd</sup> and 4<sup>th</sup> week of post lockdown and 1.8% gain in 5<sup>th</sup> week. Delhi, TN and Maharashtra gained 5.8%, 4.5% and 3.4%. The estimated mean time from onset of disease to death as observed in a study is around 17.8 days, <sup>13</sup> which roughly

corresponds to 3<sup>rd</sup> week of post lockdown for the cases which were admitted at the time of initiation of lockdown. This thus indicates that Uttarakhand did have a better control in case fatality rate in the post -lockdown period comparable to other states taken for study. This may be partly attributable to the decrease severity of cases in state as the case fatality rate is an indirect indicator of cases severity as ivermectin is hypothesized to affect the progression of disease severity if used early in disease phase. Our study observes that Uttarakhand case growth decline rate prevented minimum of 463 deaths by having early control on pandemic spread.

## **Conclusion**

The data analysis showed that Uttarakhand had a sharp fall in the active cases by 3 to 4 weeks post lockdown unlike other states and attained the active case rate of <5% in 27 days period post lockdown. The Total Positivity Rate trend in various districts showed negative linear relationship with ivermectin coverage rate in various districts of the State. Uttarakhand was also able to control the rising case fatality rate. This may have been partially due to ivermectin mass drug distribution though number of factors like population density, migration of population, strictness in lockdown, and human behavior are other contributory factors.

## **The Limitation**

In this study it is difficult to establish a link between the individual exposure to ivermectin and its effect on covid-19 as no door to door survey was undertaken for the same and the compliance to Mass Drug Intake of ivermectin cannot be ascertained.

## **Recommendations**

As this study carries the risk of ecological biasedness thus more extensive analytical studies or randomized controlled trials are needed to see the real effect of ivermectin on COVID-19 outcomes.

## **Acknowledgement**

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