Official Title

Use of Ivermectin as a Prophylactic Option in Asymptomatic Family Close Contacts with Patients of COVID-19

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جامعة الزقازيق
كلية الطب البشرى
وحده المراجعة المؤسسيه للبحث العلمى
IRB

نموذج ٨
ZU-IRB #6150/31-5-2020

NOTICE OF APPROVAL

IRB#:6150-31-5-2020
Approval DATE: 31-5-2020
Expiration DATE:31-5-2021
Principal Investigator (PI): Waheed Shouman
Title of Protocol:

Use of Ivermectin as a Prophylacitc Option in Asymptomatic Family Close Contacts for Patients with COVID -19

Dear Dr: Waheed Shouman

The IRB has reviewed and assessed the above named study regarding the potential risks and benefits based on the Declaration of Helsinki. The "ratio" of risk to benefit is reasonable, given the goals of the study. The variables assessed, including the proposed subject populations, proposed procedures and scientific background are supporting the study. The IRB approved that it is within the ethical guidelines as outlined in the Declaration of Helsinki.

Having met the requirements set forth by the Institutional Review Board by an expedited review process

your research project is now approved, effective May 31, 2020. This project will require annual review and will expire on' May 31, 2021 Research that has not received approval for continuation by this date may not continue past midnight of the expiration date.

If, during the course of the research, there are any serious adverse events, ,confidentiality concerns, these should be brought to the immediate attention of the IRB.

You should not initiate changes in the approved research protocol without IRB review and approval "except if found necessary to eliminate immediate hazards to the human subjects".

Sincerely
CHair IRB

نموذج 4 ZU- IRB #:

مراجعة اخلاقيات البحث العلمى IRB

CONFLICT OF INTEREST DISCLOSURE STATMENT

IRB#: ----------

Principal Investigator:): Prof /Waheed Shouman

Title of Protocol: Use of Ivermectin as a prophylactic option in asymptomatic family close contacts for patients with COVID-19

Each author must indicate below that either (a) no financial conflict of interest exists with any commercial entity whose products are described, reviewed, evaluated or compared in the research proposal, except for that disclosed under "Acknowledgements" or (b) a potential conflict of interest exists with one or more commercial entities whose products are described, reviewed, evaluated or compared in the research proposal through the existence of one or more of the following relationships: the author is a full or part-time employee of a company; has an existing or optional equity interest in a company; owns or partly owns patents licensed to a company; has an ongoing retainer relationship (consultant ship, speaker, etc.) with a company for which he/she receives financial remuneration; or has received financial compensation for this publication or for the work involved in this publication.

I agree with the preceding conditions and provide the appropriate signatures and information below accordingly (please photocopy this form and attach additional sheets as need be with appropriate information and signatures affixed):

PI Name:Prof Waheed Shouman

-----27-5-2020 ----------Date: Signature: Conflict of Interest: NO

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Title: Use of Ivermectin as a prophylactic option in asymptomatic family close contacts for patients with COVID-19.

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Introduction:

The 1st cases of COVID-19 were reported by the Chinese officials to the WHO by 31 December 2019. Worldwide, the total cases by 23 April 2020 are 2 ,544 ,792 confirmed cases and 175 694 deaths [1]. No consensus on a certain drug therapy for COVID-19 infection. A lot of drugs are under trial or empirically included in treatment protocols for COVID-19. Drug re-purposing is the most widely used method for rapid response in the face of this epidemic. Trials to invent denovo medicines may not be the perfect rationale, while the death and infection toll is on the rise hourly.

One of these previously FDA approved drugs is Ivermectin. Ivermectin is FDA-approved drug for Onchocerca volvulus and Lymphatic Filariasis [2]. It is known to have wide-spectrum antiviral activity against number of viruses under in vitro condition. [3-6] Ivermectin has been shown to inhibit the nuclear import of host and viral proteins. It has been demonstrated to limit infection by some RNA viruses including influenza, dengue and West Nile viruses. Ivermectin has similarly been shown to be effective against the DNA virus pseudorabies virus (PRV) both in vitro and in vivo. In an in vitro study, ivermectin was found to be an inhibitor of the SARS-CoV-2, with a single addition to Vero-hSLAM cells 2 h post infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 h. [7,8]

Rationale

Previous studies demonstrated the antiviral role of Ivermectin and preliminary results from recent experimental reports highlighted an in vitro capability of withholding SARS-CoV-2 replication

Research question

Is oral Ivermectin can prevent symptomatic COVI-19 infection in family close contacts with patients diagnosed as having the disease by RT-PCR

Hypothesis

Ivermectin has an antiviral effect and may be effective in preventing development of symptomatic infection in family close contacts with patients having COVID-19

Aim

To study oral Ivermectin as a prophylactic treatment in family close contacts with COVID-19 patients in the form of development of symptoms

Objectives

To study the effect of oral Ivermectin as a prophylactic option in contacts with COVID-19 patients

Individuals:

Adult family close contacts to COVID-19 positive patients diagnosed by RT-PCR.

Materials and Methods:

Study Design interventional study

Sample Size: Family close contacts to 50 patients diagnosed as having COVID-19 by RT-PCR

Location: Isolation facilities/Zagazig University Hospitals

Inclusion: Age more than 16 years, Asymptomatic household close contacts

Exclusion: people previously treated for COVID-19, asymptomatic contacts with who have HRCT chest done and suggestive for COVID-19 infection

Intervention :

All documented asymptomatic family contacts, starting on day of diagnosis of their index case will receive Ivermectin according to body weight as follows:

40-60 kg : 15 mg

60 -80 kg :18 mg

> 80 kg : 24 mg

This will be given as one dose at day one (diagnosis day), repeated once at day 3

In literature, individuals can receive 600mcg per Kg of ivermectin daily for 3 days without side effects (9,10)

Follow up:

1-These asymptomatic persons will be followed up for 2 weeks after the diagnosis of index case for:

Symptoms development,

Radiological evaluation if symptoms developed (HRCT chest)

Swabs for SARS-2 Virus if symptomatic

Recording possible side effects during treatment: eg sleepiness and fatigue

References:

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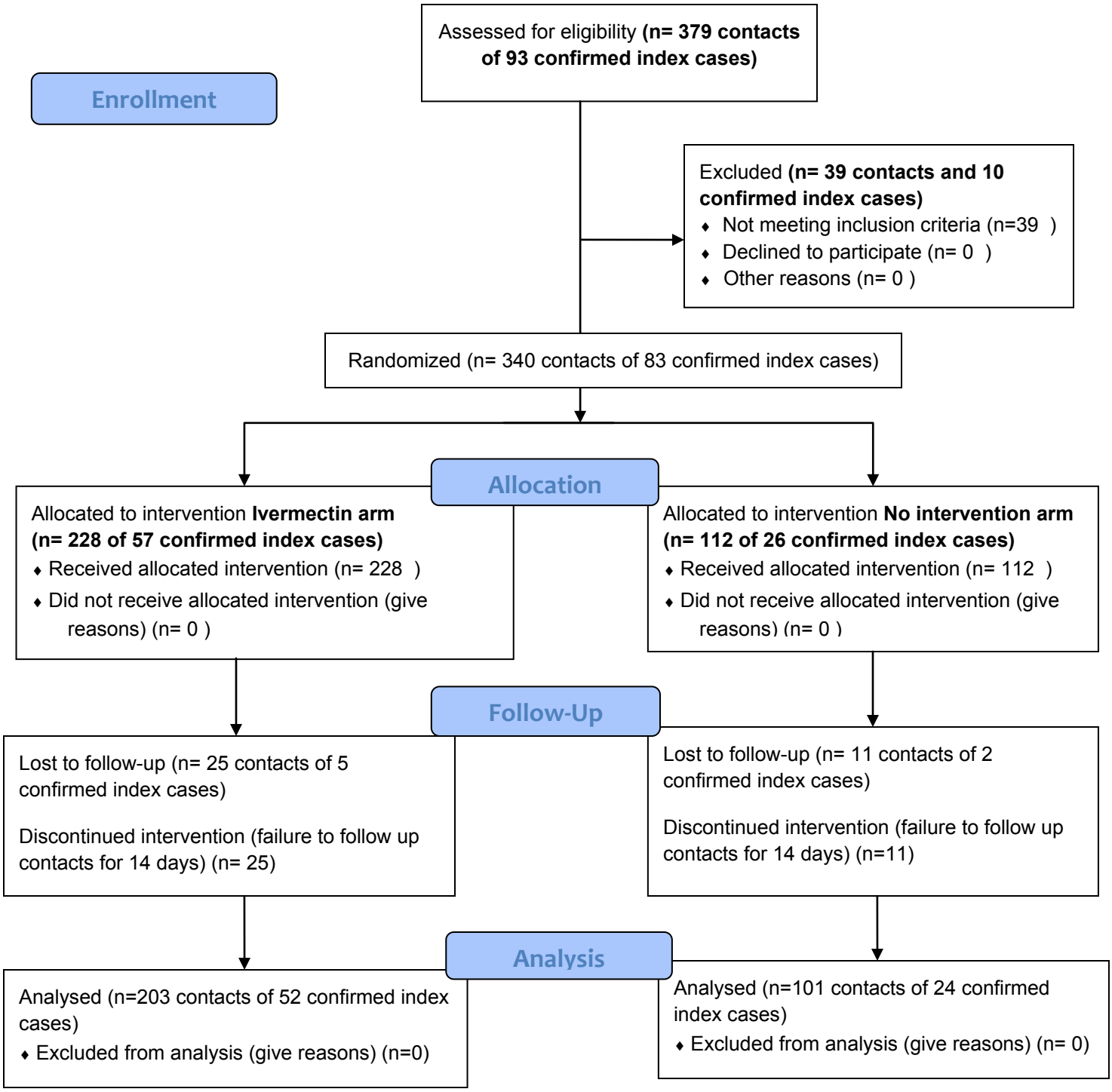
Consort Flow diagram of Ivermectin prophylaxis trial



Statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (IBM Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software Bvba, Ostend, Belgium). Continuous Quantitative variables were expressed as the mean ± SD & median (range), and categorical qualitative variables were expressed as absolute frequencies (number) & relative frequencies (percentage). Continuous data were checked for normality by using Shapiro Walk test. Mann-Whitney U test was used to compare between two groups of non-normally distributed data. Categorical data were compared using Chi-square test or Fisher's exact test when appropriate. Relative risk and its 95%Confidence interval (CI) was calculated to estimate risk of COVID-19 infection in addition forest plot was plotted. Univariate and multivariate binary logistic regression were built to find predictors for COVID-19 protection. All tests were two sided. p-value < 0.05 was considered statistically significant.

Results

As regard index cases, there were 9 (11.8%) mild , 44 (57.9%) moderate and 23 (30.3%) severe cases. In the ivermectin group, there were 8 (53.3%) mild , 6 (40%) moderate and 1 (6.7%) severe cases. While in the no-intervention group, there were 31 (52.5) mild, 21 (35.6%) moderate and 7 (11.9%) cases.

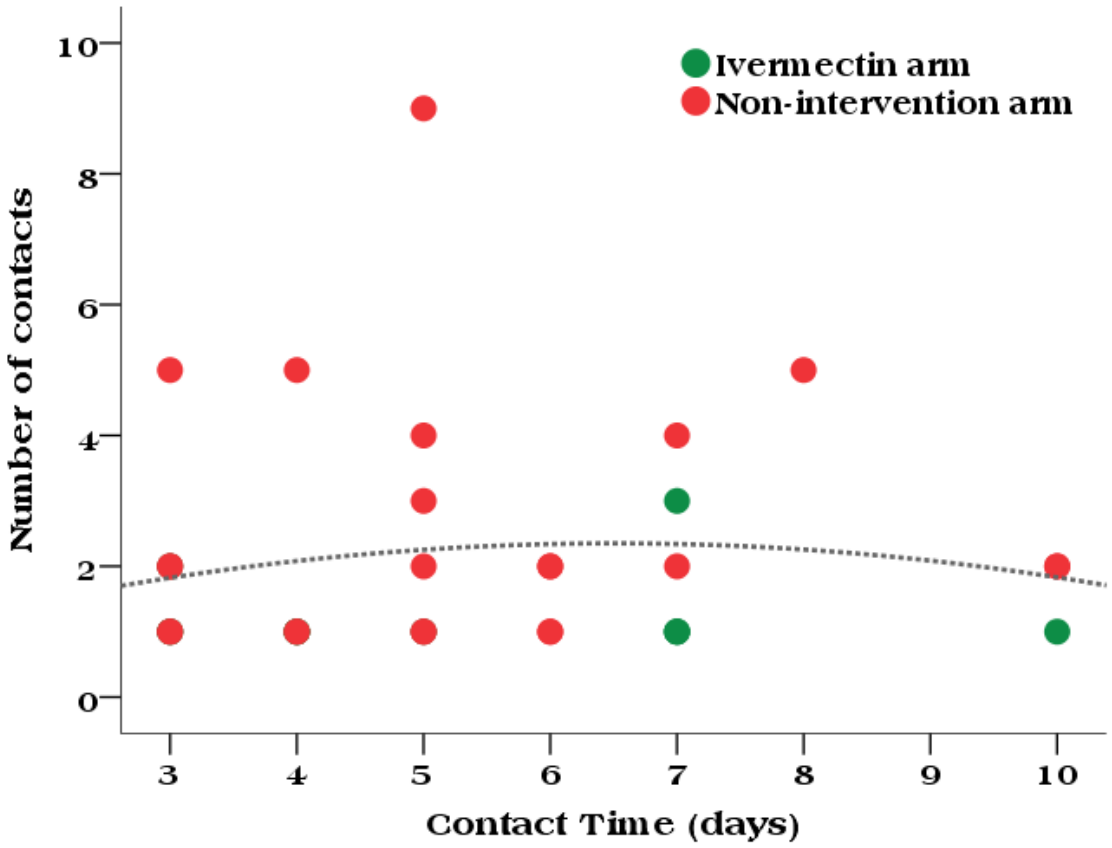


Figure (1): Scatter plot shows relationship between contact time in days and number of contacts that developed COVID-19; dashed line represent best fitted line (quadratic model).

There was insignificant linear correlation between contact time in days and number of contact that developed COVID-19. The appropriate forecasting for number of contact that developed COVID-19 based upon contact time in days was quadratic model.

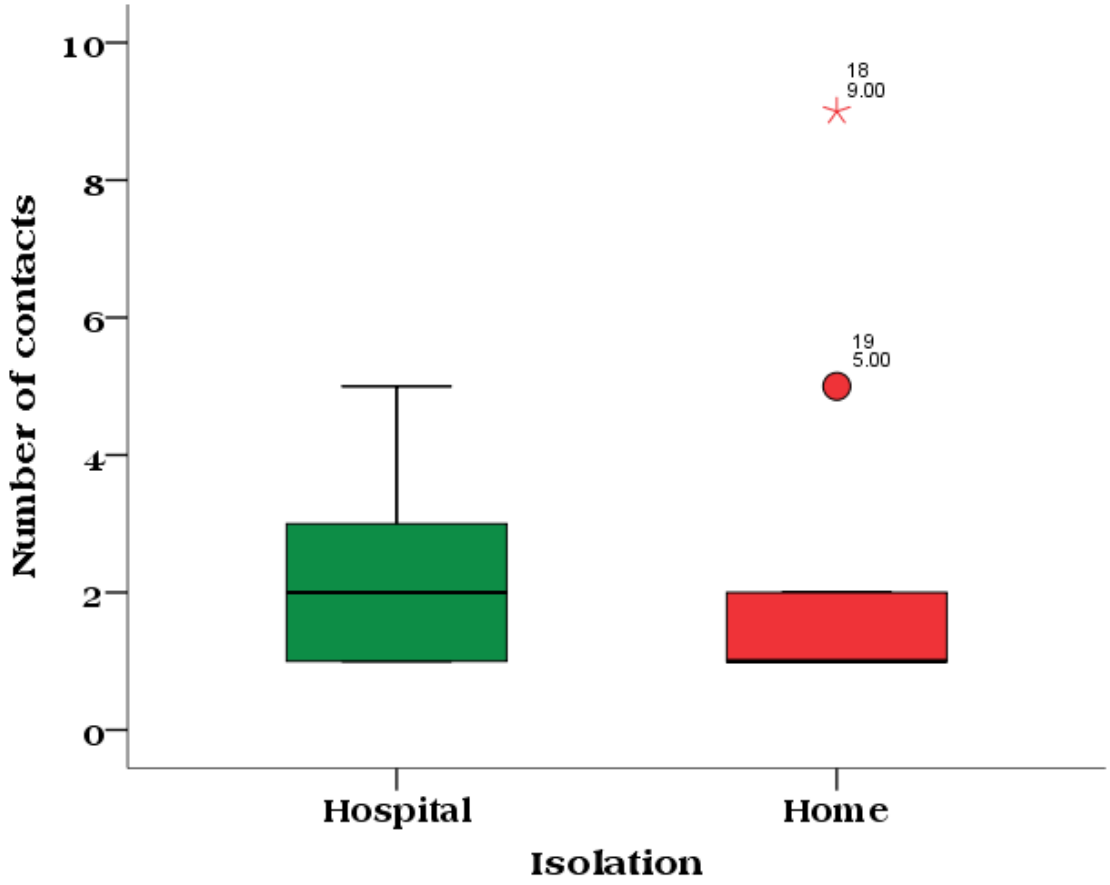


Figure (2): Box plot shows relationship between isolation and number of contacts that developed COVID-19.

There was insignificant difference between index cases isolated at hospital and index cases isolated at home regarding number of contact that developed COVID-19 where mean number of contact that developed COVID-19 (±SD) was 2.14 (±1.35) versus 2.07 (± 2.26) respectively (p-value=0.280)

Table (1): Comparison between Ivermectin arm and non-intervention arm regarding basic characteristics.

Basic characteristics	Ivermectin arm (N=203)		Non-intervention arm (N=101)		Test	p-value
	No.	%	No.	%		
Gender						
Male	106	52.2%	50	49.5%	0.199a	0.656
Female	97	47.8%	51	50.5%		
Age (years)						
Mean ± SD	39.75 ± 14.93		37.69 ± 16.95		-	0.175
Median (Range)	38 (16 – 94)		35 (16 – 78)		1.357 b	
Any comorbidity						
Absent	156	76.8%	75	74.3%	0.248a	0.619
Present	47	23.2%	26	25.7%		

a: Chi-square test; b: Mann Whitney U test; p< 0.05 is significant.

Table (1) shows that there was no significant difference between both arms as regard gender, age or comorbidities. The median (range) age for both groups was 38 (16-94) and 35 (16-78) years respectively.

The most common comorbidities were; hypertension in 16 (7.9%) and 13 (12.9%), DM in 13 (6.4%) and 10 (9.9%), bronchial asthma in 7 (3.4%) and 2 (2%), ischemic heart disease in 6 (3%) and 1 (1%), hypothyroidism in 5 (2.5%) and 1 (1%), chronic kidney disease in 2 (1%) and 1 (1%), liver

cirrhosis in 1 (0.5%) and 1 (1%), cardiomyopathy in 2 (1%) and 0% in both ivermectin and no-intervention group respectively.

Table (2): Comparison between Ivermectin arm and non-intervention arm regarding outcome.

Outcome	Ivermectin arm (N=203)		Non-intervention arm (N=101)		Test	p-value
	No.	%	No.	%		
Symptoms						
Absent	188	92.6%	42	41.6%	95.351 a	<0.001
Present	15	7.4%	59	58.4%		
Days until symptoms						
Mean ± SD	3 ± 1.30		4.13 ± 1.78		-2.391b	0.017
Median (Range)	2 (2 – 6)		4 (2 – 10)			
2 days	8	53.3%	12	20.3%	10.150 a	0.118
3 days	2	13.3%	13	22%		
4 days	3	20%	11	18.6%		
5 days	1	6.7%	13	22%		
6 days	1	6.7%	1	1.7%		
7 days	0	0%	8	13.6%		
10 days	0	0%	1	1.7%		

CT suspect						
Negative	7	50%	30	51.7%	0.013a	>0.05
Positive	7	50%	28	47.3%		
CBC suspect						
Negative	2	14.3%	5	8.6%	0.412 a	>0.05
Positive	12	85.7%	53	91.4%		
Protection rate						
No protection	15	7.4%	59	58.4%	95.351 a	<0.001
Protection	188	92.6%	42	41.6%		

a: Chi-square test; b: Mann Whitney U test; p< 0.05 is significant.

Table (2) shows that 15 contacts (7.4%) developed COVID-19 in the ivermectin arm compared to 59 (58.4%) in the no-intervention arm, all of them were symptomatic, according to the study protocol . The difference was highly significant (p<0.001). The median (range) days for developing the disease was 2 (2-6) in ivermectin group compared and 4 (2-10) in the no-intervention group, the difference was significant (p<0.017). Ten contacts (66.6%) developed symptoms in 1st 3 days in ivermectin group, and none developed it after 6 days. In the no-intervention arm, 25 (42.3%) developed symptoms in the 1st 3 days and continued to the 10 days.

HRCT of the chest was performed in 14 out 15 contacts and in 58 of the 59 contacts who developed symptoms in ivermectin and no-intervention groups, respectively. The missed one case in each arm had symptoms and positive RT-PCR without other investigations. Chest HRCT was positive for

COVID-19 in 7 (50%) and 28 (48.3%) in ivermectin and no-intervention groups, respectively.

Complete blood count was performed also in 14 and 58 contacts who developed symptoms in ivermectin and no-intervention groups respectively. Positive criteria in CBC was present in 12 (85.7%) and 53 (91.4%) in ivermectin and no-intervention groups respectively.

Table (3): Comparison between Ivermectin arm and non-intervention arm regarding protection rate stratified by basic characteristics.

		Protection rate			
		Ivermectin arm	Non-intervention arm	Testa	p-value
All patients		92.6%	41.6%	------	------
Index case severity	Mild	92.9%	35%	11.381	0.001
	Moderate	95.6%	55.8%	42.666	<0.001
	Severe	85.2%	28.9%	29.928	<0.001
Age	≤60	93.8%	41.3%	91.514	<0.001
	>60	84%	44.4%	5.320	0.034
Gender	Male	94.3%	42%	53.482	<0.001
	Female	90.7%	41.2%	42.278	<0.001
Any comorbidity	No	95.5%	45.3%	77.474	<0.001
	Yes	83%	30.8%	19.899	<0.001

DM	No	94.7%	42.9%	96.308	<0.001
	Yes	61.5%	30%	2.253	0.214
HTN	No	93%	44.3%	81.372	<0.001
	Yes	87.5%	23.1%	12.272	<0.001

a: Chi-square test; p< 0.05 is significant.

Table (3) shows that 7.4% contacts developed diseases in ivermectin group while they were 58.4% in no-intervention group. Contacts tend to be infected when the index case was severe; 14.8% and 71.1% in both groups, respectively. The protection rate for ivermectin was more prominent in contacts less than 60 years old (6.2% infected compared to 58.7% if no intervention) , but still effective in elder than 60 years (16% infected compared to 55.6% if no intervention).

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Table (4): Predictors for COVID-19 protection.

	Univariate Model		Multivariate Model	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Arm				
Ivermectin	12.533 (7.408-21.205)	<0.001	11.445 (4.444-29.475)	<0.001
Non-intervention	Reference			
Index case severity		<0.001		0.018
Mild	1.429 (0.722-2.828)	0.306	1.257 (0.486-3.247)	0.637
Moderate	6.120 (4.010-9.341)	<0.001	2.816 (1.355-5.851)	0.006

Severe	Reference			
Age				
Age≤60 years	3.154 (2.386-4.169)	<0.001	0.254 (0.101-0.639)	0.004
Age>60 years	Reference			
Gender				
Male	3.457 (2.373-5.036)	<0.001	0.836 (0.437-1.600)	0.588
Female	Reference			
Any comorbidity				
Absent	3.812 (2.774-5.239)	<0.001	2.222 (0.967-5.108)	0.060
Present	Reference			

OR: Odds Ratio; 95%CI: 95%Confidence Interval.

Table (5) shows that ivermectin have very highly significant role in the protection of SARS-CoV-2 infection. . It has an OR of 12.533 and 11.445 when compared to no intervention in both univariate and multivariate models, respectively. Ivermectin protection was not affected by gender or comorbidities in multivariate model.

As regard ivermectin side effects, they were reported in 11 (5.4%) contacts. These were; diarrhea (1.5%), nausea (1%), fatigue (1%), sleepiness (0.5%), abdominal pain (0.5%), heart burn (0.5%), tingling and numbness (0.5%) and lastly burning sensation (0.5%)