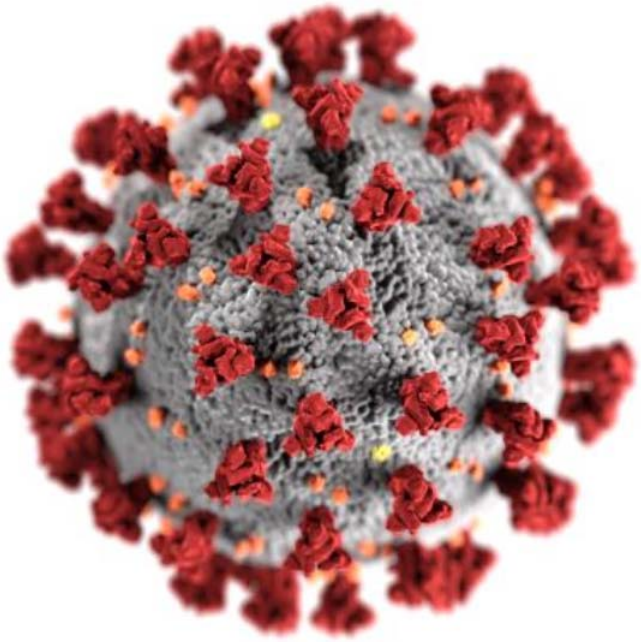
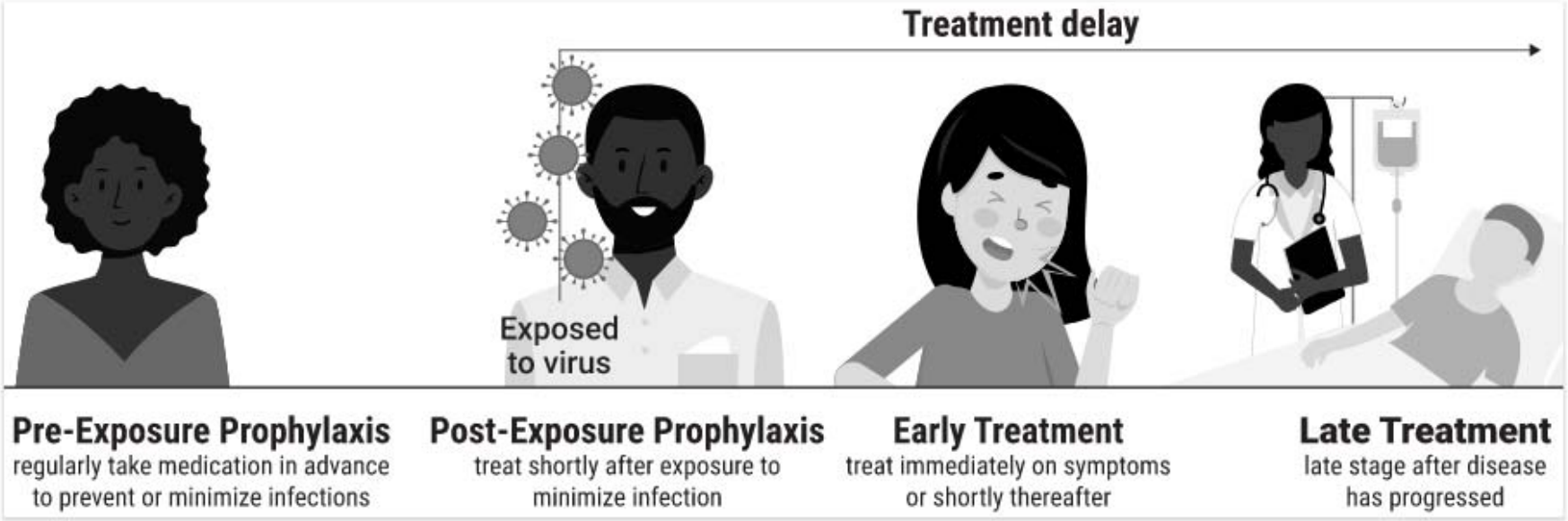


COVID-19

Rx Meta-analysis

Let the Data Speak

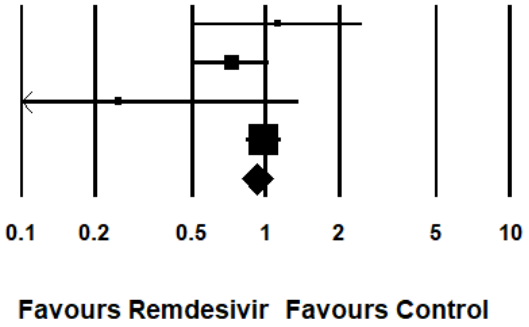
Paul E Marik, MD,FCCM,FCCP


Treatment delay
Exposed
to virus
Pre-Exposure Prophylaxis
regularly take medication in advance
to prevent or minimize infections
Post-Exposure Prophylaxis
treat shortly after exposure to
minimize infection
Early Treatment
treat immediately on symptoms
or shortly thereafter
Late Treatment
late stage after disease
has progressed

Remdesivir: In-hospital RCTs

Mortality

	Statistics for each study					Dead / Total	
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Group-Remdesivir	Group-Control
Wang	1.116	0.501	2.488	0.269	0.788	22 / 158	10 / 79
Beigel	0.724	0.507	1.035	-1.773	0.076	62 / 541	79 / 521
Spinner	0.249	0.045	1.370	-1.599	0.110	2 / 396	4 / 200
SOLIDARITY	0.978	0.826	1.159	-0.254	0.800	301 / 2743	303 / 2708
	0.922	0.794	1.071	-1.057	0.290		

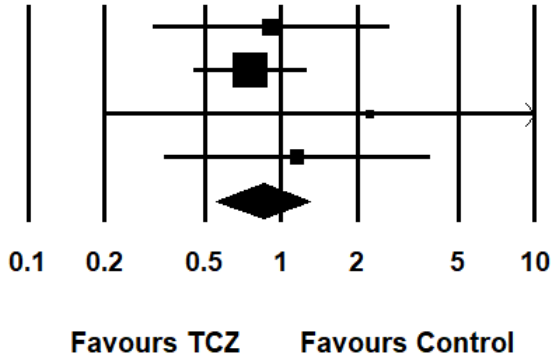


Meta Analysis

Tocilizumab: In-hospital RCTs

Mortality

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Deaths / Total Group-TCZ	Deaths / Total Group-Control
Hermine	0.906	0.308	2.661	-0.180	0.857	7 / 64	8 / 67
Rosas	0.755	0.451	1.262	-1.072	0.284	58 / 294	28 / 114
Salvarani	2.241	0.198	25.369	0.652	0.514	2 / 60	1 / 66
Stone	1.155	0.345	3.868	0.233	0.816	9 / 161	4 / 82
	0.847	0.553	1.297	-0.764	0.445		

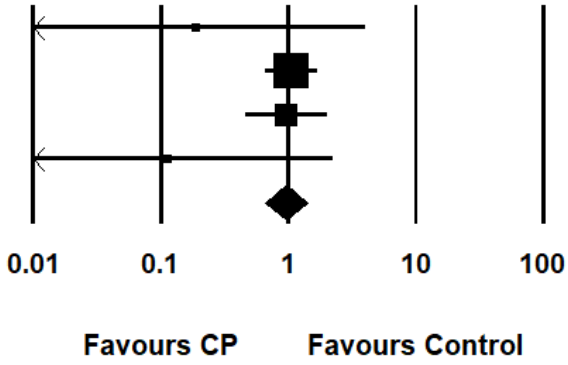


Meta Analysis

Convalescent Plasma: In-hospital RCTs

Mortality

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Deaths / Total Group-CP	Deaths / Total Group-Ctl
Li	0.189	0.009	4.026	-1.068	0.285	0 / 52	2 / 51
Agarwal	1.056	0.660	1.691	0.228	0.820	44 / 235	41 / 229
Simonovich	0.954	0.460	1.982	-0.125	0.900	25 / 228	12 / 105
Avendano-Sola	0.114	0.006	2.190	-1.440	0.150	0 / 38	4 / 43
	0.960	0.651	1.417	-0.203	0.839		

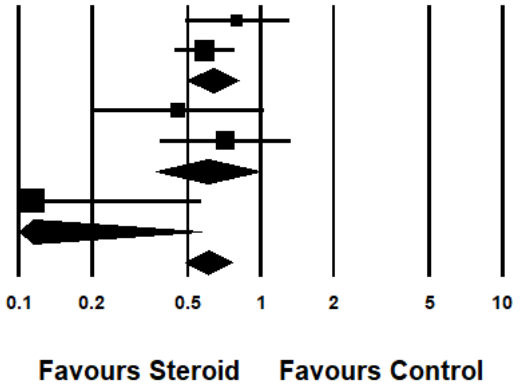


Meta Analysis

Corticosteroids: In-hospital RCTs

Mortality

Group by Steroid	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Death / Total Group-Steroid	Death / Total Group-Control
Dexa	CoDEX	0.800	0.488	1.313	-0.882	0.378	69 / 128	76 / 128
Dexa	RECOVERY	0.586	0.442	0.779	-3.690	0.000	95 / 324	283 / 683
Dexa		0.633	0.495	0.810	-3.641	0.000		
HC	CAPE COVID	0.455	0.200	1.035	-1.878	0.060	11 / 75	20 / 73
HC	REMAP-CAP	0.715	0.383	1.335	-1.053	0.292	26 / 105	29 / 92
HC		0.606	0.369	0.996	-1.975	0.048		
MP	Edalatifard	0.115	0.023	0.563	-2.667	0.008	2 / 34	12 / 34
MP		0.115	0.023	0.563	-2.667	0.008		
Overall		0.608	0.489	0.756	-4.466	0.000		

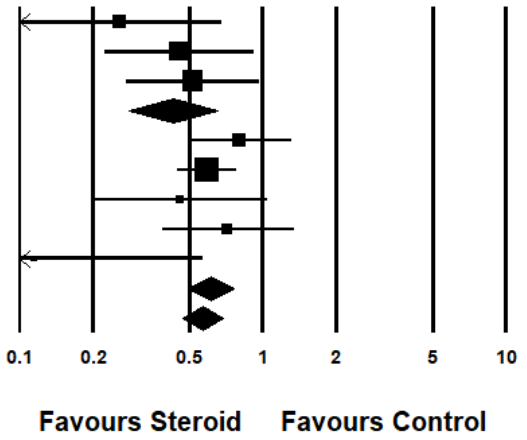


Meta Analysis

Corticosteroids: In-hospital RCTs & Obs

Mortality

Group by RCT-Obs	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Death / Total Group-Steroid	Death / Total Group-Control
Obs	Salton	0.256	0.098	0.671	-2.771	0.006	6 / 83	21 / 90
Obs	Fadel	0.451	0.223	0.911	-2.220	0.026	18 / 132	21 / 81
Obs	Fernandez-Cruz	0.514	0.274	0.965	-2.071	0.038	55 / 396	16 / 67
Obs		0.429	0.282	0.654	-3.931	0.000		
RCT	CoDEX	0.800	0.488	1.313	-0.882	0.378	69 / 128	76 / 128
RCT	RECOVERY	0.586	0.442	0.779	-3.690	0.000	95 / 324	283 / 683
RCT	CAPE COVID	0.455	0.200	1.035	-1.878	0.060	11 / 75	20 / 73
RCT	REMAP-CAP	0.715	0.383	1.335	-1.053	0.292	26 / 105	29 / 92
RCT	Edalatifard	0.115	0.023	0.563	-2.667	0.008	2 / 34	12 / 34
RCT		0.608	0.489	0.756	-4.466	0.000		
Overall		0.565	0.465	0.686	-5.773	0.000		



Meta Analysis

Corticosteroids: In-hospital RCTs & Obs

Mortality

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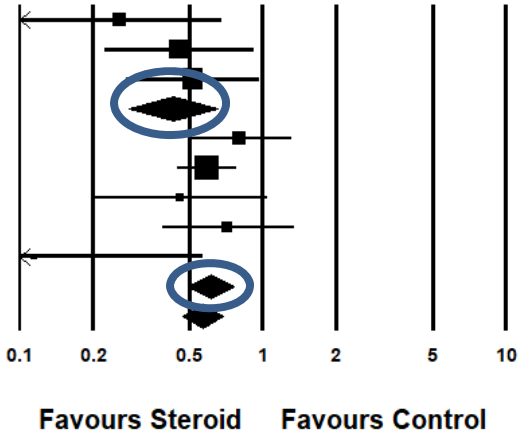
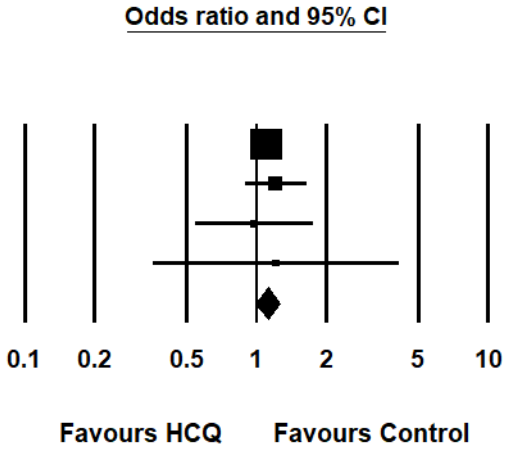


Meta Analysis

Hydroxychloroquine: In-hospital RCTs

Mortality

	Statistics for each study					Deaths / Total	
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Group-HCQ	Group-Control
RECOVERY	1.106	0.963	1.269	1.428	0.153	421 / 1561	790 / 3155
SOLIDARITY	1.207	0.892	1.635	1.218	0.223	104 / 947	84 / 906
Self	0.977	0.544	1.755	-0.078	0.938	25 / 242	25 / 237
Abd-Elsalan	1.213	0.358	4.116	0.310	0.757	6 / 97	5 / 97
	1.116	0.988	1.261	1.769	0.077		

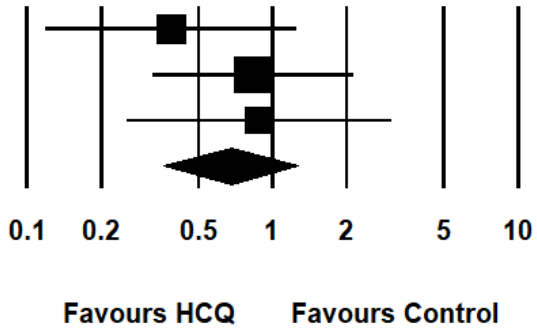


Meta Analysis

Hydroxychloroquine: Outpatient RCT's

Hospitalization

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Events / Total HCQ	Events / Total Control
Skipper	0.387	0.119	1.252	-1.585	0.113	4 / 212	10 / 211
Mitja	0.830	0.324	2.126	-0.389	0.697	8 / 136	11 / 157
Omrani	0.878	0.253	3.047	-0.205	0.838	7 / 302	4 / 152
	0.675	0.358	1.270	-1.219	0.223		

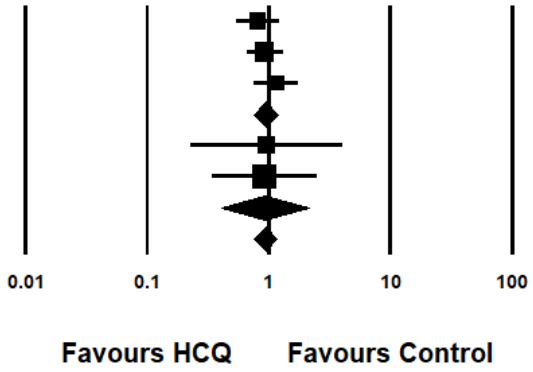


Meta Analysis

Hydroxychloroquine: Prophylaxis

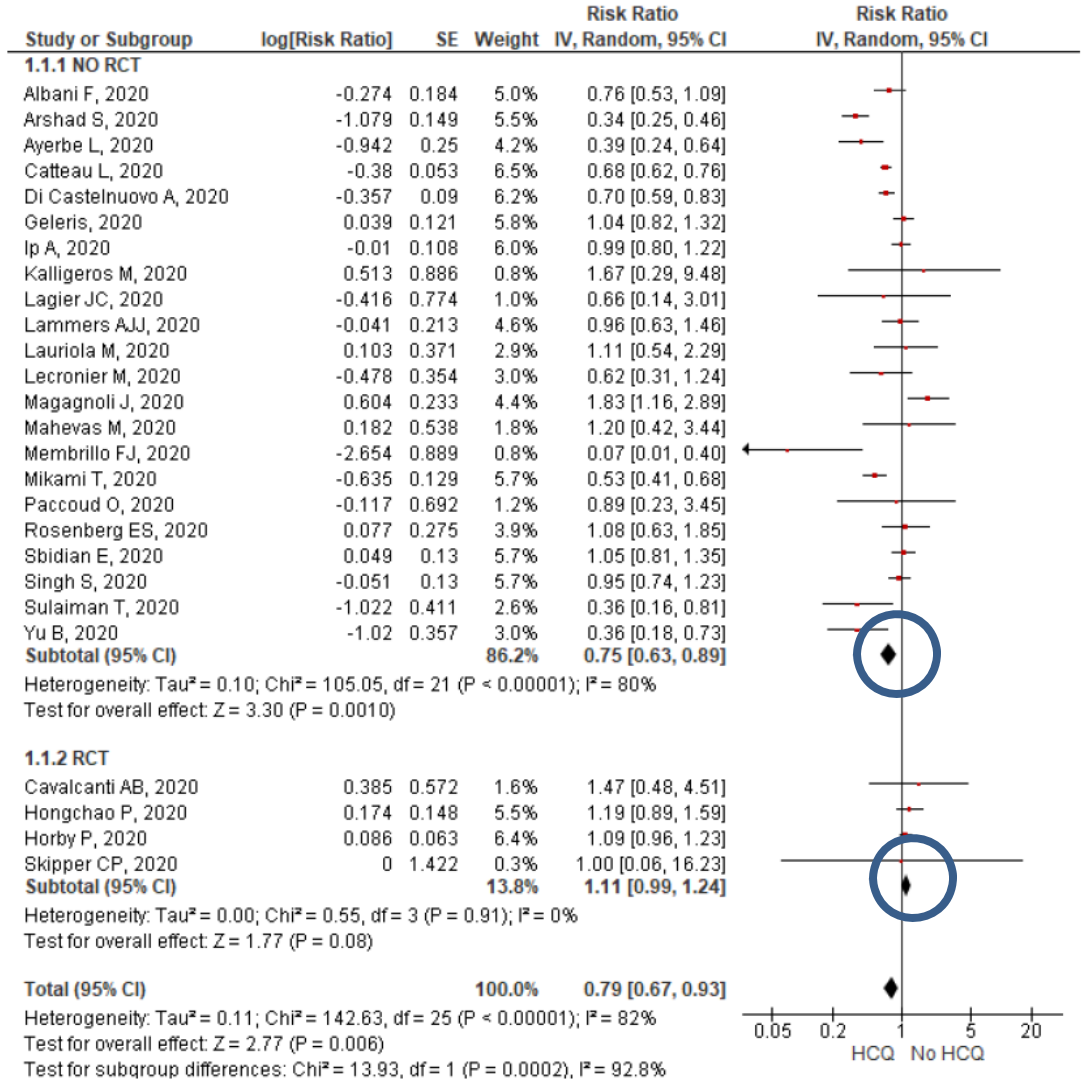
PCR Confirmed Infections

Group by Type		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	PCR infection / Total: Group-HCQ	PCR infection / Total: Group-Control
Post-exposure	Boulware	0.808	0.537	1.214	-1.026	0.305	49 / 414	58 / 407
Post-exposure	Mitja	0.922	0.653	1.302	-0.459	0.646	64 / 1116	74 / 1196
Post-exposure	Barnabas	1.142	0.744	1.754	0.609	0.543	53 / 353	45 / 336
Post-exposure		0.940	0.751	1.176	-0.545	0.586		
Pre-exposure	Abella	0.950	0.227	3.980	-0.070	0.944	4 / 64	4 / 61
Pre-exposure	Rajasingham	0.915	0.336	2.488	-0.174	0.862	11 / 989	6 / 494
Pre-exposure		0.926	0.408	2.104	-0.183	0.855		
Overall		0.939	0.756	1.165	-0.574	0.566		



Meta Analysis

Low dose hydroxychloroquine is associated with lower mortality in COVID-19: a meta-analysis of 26 studies and 44,521 patients

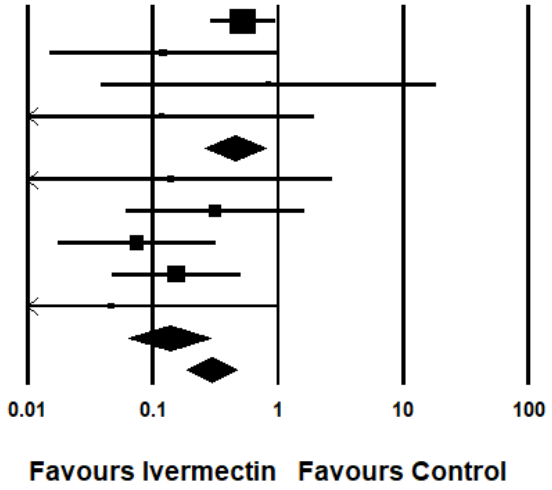


Di Castelnuovo A, et al. med Rxiv 2020

Ivermectin: Acute Infections

Mortality

Group by RCT-Obs	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Ivermectin Dead / Total	Control Dead / Total
OBS	Rajter	0.524	0.287	0.958	-2.099	0.036	26 / 173	27 / 107
OBS	Khan	0.121	0.015	0.969	-1.990	0.047	1 / 115	9 / 133
OBS	Gorial	0.842	0.039	18.393	-0.109	0.913	0 / 16	2 / 71
OBS	Budhiraja	0.118	0.007	1.932	-1.499	0.134	0 / 34	103 / 942
OBS		0.451	0.258	0.789	-2.793	0.005		
RCT	Mahmud	0.138	0.007	2.694	-1.306	0.192	0 / 183	3 / 180
RCT	Hashim	0.314	0.061	1.611	-1.389	0.165	2 / 70	6 / 70
RCT	Elgazzar	0.074	0.017	0.318	-3.502	0.000	2 / 200	24 / 200
RCT	Niaee	0.154	0.047	0.506	-3.080	0.002	4 / 120	11 / 60
RCT	Cadegiani	0.046	0.002	0.970	-1.980	0.048	0 / 585	2 / 137
RCT		0.136	0.064	0.288	-5.207	0.000		
Overall		0.294	0.188	0.461	-5.347	0.000		



Meta Analysis

Ivermectin: Acute Infections

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OBS	Rajter	0.524	0.287	0.958	-2.099	0.036	26 / 173	27 / 107
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RCT	Elgazzar	0.074	0.017	0.318	-3.502	0.000	2 / 200	24 / 200
RCT	Niaee	0.154	0.047	0.506	-3.080	0.002	4 / 120	11 / 60
RCT	Cadegiani	0.046	0.002	0.970	-1.980	0.048	0 / 585	2 / 137
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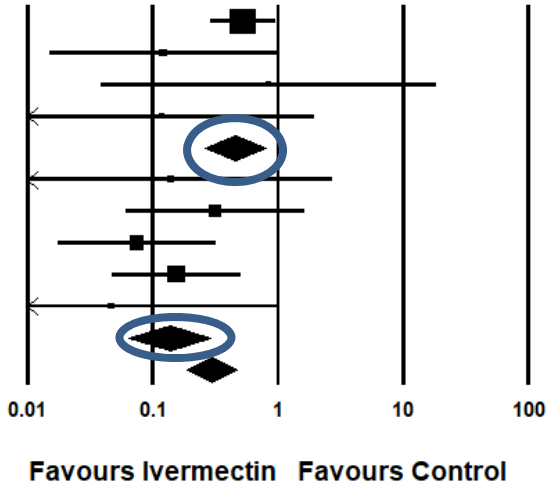
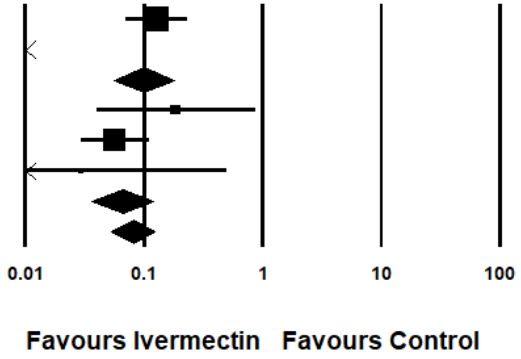


Meta Analysis

Ivermectin: Prophylaxis

Symptomatic infections

Group by Type	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Symptomatic Infection / Total: Group-Ivermectin	Symptomatic Infection / Total: Group-Control
Obs	Behera	0.127	0.069	0.232	-6.704	0.000	15 / 91	171 / 281
Obs	Carvallo- 2	0.000	0.000	0.007	-5.426	0.000	0 / 788	237 / 407
Obs		0.099	0.055	0.178	-7.703	0.000		
RCT	Elgazzar	0.184	0.039	0.861	-2.150	0.032	2 / 100	10 / 100
RCT	Shouman	0.057	0.029	0.110	-8.542	0.000	15 / 203	59 / 101
RCT	Carvallo -1	0.029	0.002	0.497	-2.441	0.015	0 / 131	11 / 98
RCT		0.066	0.036	0.118	-9.019	0.000		
Overall		0.080	0.053	0.122	-11.822	0.000		



Meta Analysis

Ivermectin: Prophylaxis

Symptomatic infections

Group by Type	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Symptomatic Infection / Total: Group-Ivermectin	Symptomatic Infection / Total: Group-Control
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Post-exposure	Shouman	0.057	0.029	0.110	-8.542	0.000	15 / 203	59 / 101
Post-exposure		0.068	0.037	0.125	-8.701	0.000		
Pre-exposure	Behera	0.127	0.069	0.232	-6.704	0.000	15 / 91	171 / 281
Pre-exposure	Carvallo -1	0.029	0.002	0.497	-2.441	0.015	0 / 131	11 / 98
Pre-exposure	Carvalllo-2	0.000	0.000	0.007	-5.426	0.000	0 / 788	237 / 407
Pre-exposure		0.094	0.053	0.167	-8.038	0.000		
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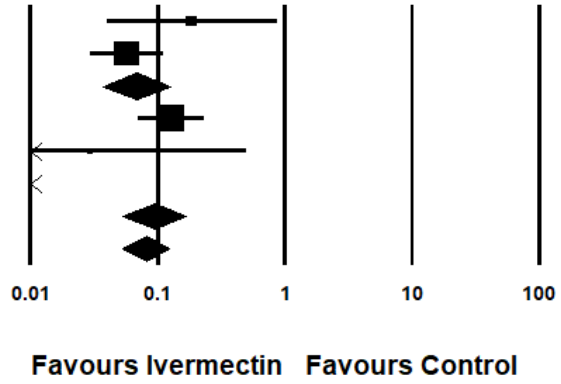
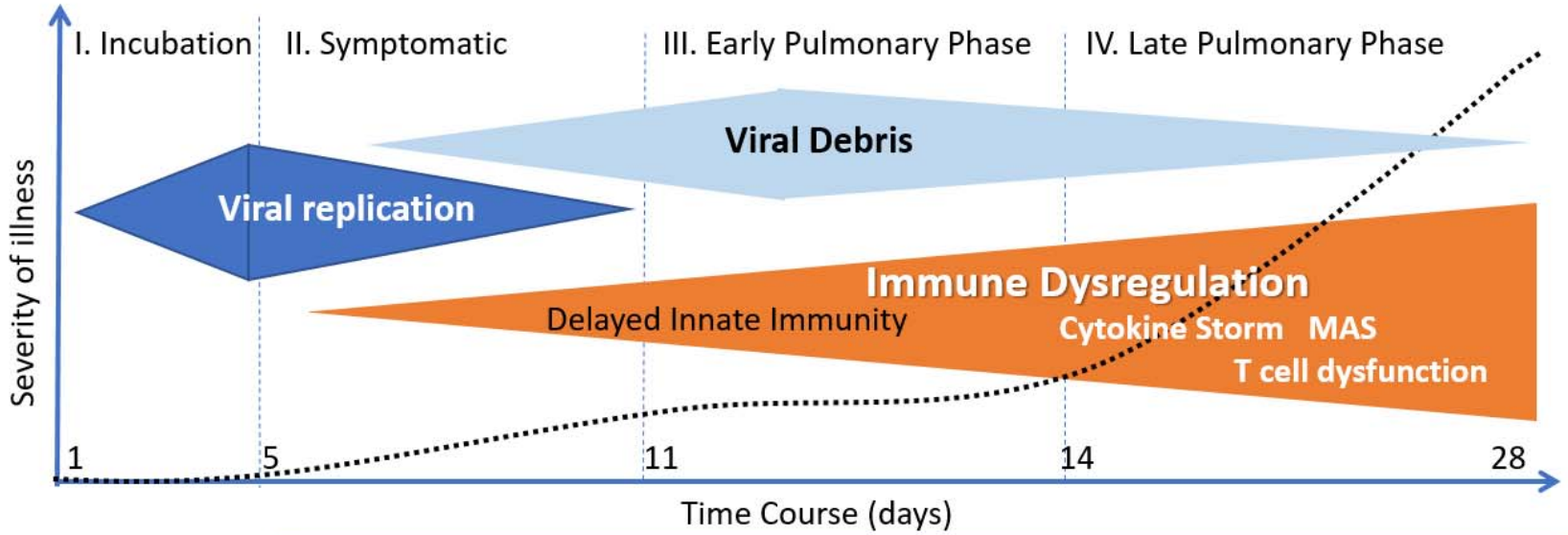


Meta Analysis

Failed and Successful Rx for COVID-19 by Phase of Illness

	Pre-exposure/ Post-Exposure/ Incubation	Symptomatic Phase	Pulmonary/ inflammatory phase
Hydroxychloroquine	Unclear benefit	No benefit	?Trend to harm
Remdesivir	n/a	?? Reduced time to recovery No mortality benefit	No benefit
Lopivinar-Ritonavir	n/a	No benefit	No benefit
Interferon α/β	Inhaled ? Benefit	No benefit	?Trend harm
Tocilizumab	n/a	n/a	No Benefit
Convalescent Serum	n/a	Unlikely	No Benefit
Corticosteroids	n/a	Trend to harm	BENEFIT
Ivermectin	BENEFIT	BENEFIT	BENEFIT

Time Course and approach to Rx



Ground-glass infiltrates	+	++	+++ ++++
Clinical Symptoms	Fever, malaise, cough, headache, diarrhea	SOB – Mild hypoxia ≤4 L/min N/C & aSat < 94%	Progressive hypoxia
Treatment approach	Antiviral Rx	Anti-inflammatory Rx	
Potential therapies	? Interferon-α	Methylprednisolone 40mg q 12 inc. to 80 mg q 12 if reqd.	
	ASA	Enoxaparin 60 mg/day	Enoxaparin 1mg/kg s/c q 12
	IVERMECTIN 12mg	IVERMECTIN 12mg x 2	
	Quercetin + Zinc + Vit C + Vit D	Quercetin + Zinc + Vitamin D + IV Vitamin C	


Thank you