Supplementary Statistical Appendix for: Large-scale artemisinin + piperaquine mass drug administration with or without primaquine dramatically reduces malaria in a highly-endemic region of Africa

Summary

This supplement gives fuller details of the statistical analyses. In Section 1 we give methods for calculating the crude monthly rates and for calculating confidence intervals and performing tests on the rates through quasi-Poisson models. In Section 2 we gives the results of the main analyses on the incidence rates including the definition of treatment effectiveness. In Section 3 we give more details on the rate analyses including a data listing. Finally, in Section 4 we give the analysis from Table 2.

1 Statistical Methods on Incidence Data

We modeled the rate of incident cases in a month per person using data from Supplemental Table 3 with populations from Table 1 and using 420,000 for the Grand Comore Island population. We calculate the crude monthly rate per 100,000 for each group (AP+PMQ$_{LD}$, AP alone, or No MDA) by assuming stable populations from 2012-2013 and using the total incident cases in the area and time period divided by the total person-months under observation for that group. This is equivalent to the weighted average of the mean observed monthly rates per district, with the weights equal to the population of the district divided by the total populations in all districts within that group.

To calculate confidence intervals and perform tests, we use a quasi-Poisson model (also called an overdispersed Poisson model, or a count model with extra-Poisson variation) to account for variability due to clustering. The model has main effects for district, month, and treatment, with offsets for population so that we modeled effects on rates instead of counts. The quasi-Poisson model automatically accounts for possible model misspecification through an overdispersion parameter. We used only data from April 2012-September 2012 (as the baseline) and April 2013 to September 2013 (as the post-treatment period), and the treatment effects (including that of the control 'No MDA' treatment in Grand Comore Island) were only measured during the post-treatment period. Because we do not include a year effect, some of the treatment effect from the model may be due to other changes from 2012 to 2013 (e.g., change in the force of infection); however, since there was no MDA in the Grand Comore Island, that group partially serves as a control of the year effect. If the apparent treatment effects in the AP and AP+PMQ$_{LD}$ groups are much stronger than the apparent 'treatment' effect in the No MDA group, then this would strongly suggest that the AP and AP+PMQ$_{LD}$ treatments are in fact effective. We tested for contrasts between the treatment groups using Wald tests. To calculate how many times we would need to repeat the experiment to get enough information

to show that the ratios are between $(0.80, 1.25)$, we divide the variance of the contast by a factor such that either the lower 95% confidence limit equals 0.80 or the upper 95% coonfidence limit euqal 1.25, and take the maximum of the two factors. Calculations were done using the glm function in R Version 3.4.1.

2 Main Results on Incidence Data

We define a baseline period (April 2012 to September 2012) and a post-treatment period one year later (April 2013 to September 2013). Here are the crude monthly incidence rates per 100,000 for 2012 and 2013 (only in the months April to September):

- For the districts that were treated with AP+PMQ$_{LD}$, the rates were 310.8 in 2012 and 2.06 in 2013.
- For the districts that were treated with AP the rates were 412.1 in 2012 and 2.6 in 2013.
- For the Comore Island were no MDA was done, the rates were 1446.4 in 2012 and 1044.6 in 2013.

Using a quasi-Possion model, we estimate the change in incidence rates from baseline to post-treatment after controling for district and month of infection. We present the results as the modeled proportion of the baseline rate for the three treatment groups (AP+PMQ$_{LD}$, AP, and No MDA). We give 95% confidence intervals and two-sided p-values testing whether the effects are different from 1. Here are the results in table form (see Figure 1 for the results as a figure):

	Estimate	lower95pctCL	upper95pctCL	p.value
AP.PMQ	0.00662	0.00017	0.03618	p=0.00007
AP	0.00631	0.00109	0.01928	p<.00001
NoMDA	0.72221	0.67656	0.77077	p<.00001

This means that the estimate of the average incident rate in the Grand Comore Island (the No MDA group) in 2013 is about 72.2% (95% CI: 67.7%, 77.1%; p<.00001) of the 2012 rate. So there is a substantial significant drop in incidence rates from 2012 to 2013. But the effects in the two active treatment groups (AP+PMQ$_{LD}$ and AP) a quite a bit stronger. The estimate of the average incident rate in the districts treated with AP+PMQ$_{LD}$ in 2013 is about 0.66% (95% CI: 0.02%, 3.62%; p=0.00007) of the 2012 rate. Similarly, the estimate of the average incident rate in the districts treated with AP only in 2013 is about 0.63% (95% CI: 0.11%, 1.93%; p<.00001) of the 2012 rate.

Analogously to the way vaccine effectiveness is defined (see e.g., [1]), we define the treatment effectiveness as 1 minus the ratio of effect under treatment over effect under no treatment, where we measure the effects using the modeled post-treatment rate as a percentage of baseline rate (see Figure 1). We

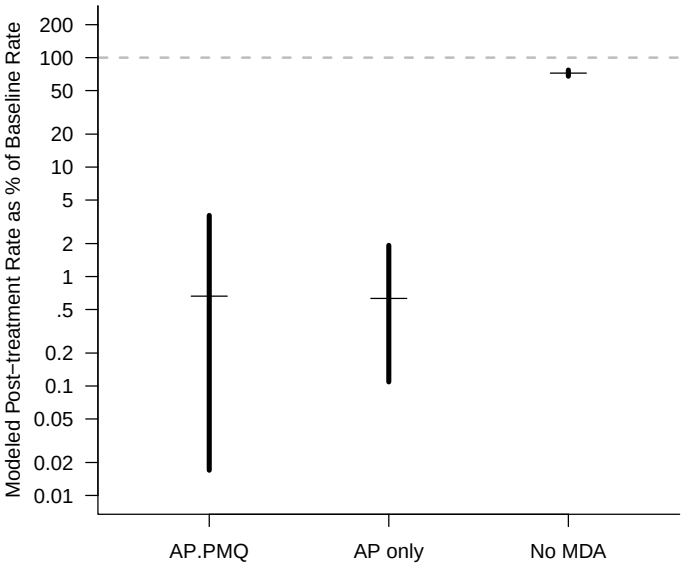

Figure 1: Modeled post-treatment rate as a percentage of baseline rate in the three treatment groups. Estimates are horizontal bars, and 95% confidence intervals are vertical bars.

estimate the treatment effectiveness of AP+PMQ$_{LD}$ (using the No MDA group as the no treatment group) as 1 - 0.0066/0.722 = 0.99083 (95% CI: 0.90531, 0.99911), which is significantly different from 0 (p=0.00008). Similarly, we estimate the treatment effectiveness of AP only as 1-0.0063/0.722 = 0.99127 (95% CI: 0.96571, 0.99778), which is significantly different from 0 (p<.00001). Note that although we assumed a stable population, because the treatment effectiveness is based on a ratio of rate ratios, the treatment effectiveness would not change if all the populations changed by the same factor from 2012 to 2013. For example, if all districts as well as the Grand Comore Island had a 1% growth in population from 2012 to 2013 and we adjusted the population offsets accordingly, the treatment effectiveness values and the associated confidence intervals would not change.

We compare AP+PMQ$_{LD}$ to that of AP in terms of post-treatment rates as a percentage of baseline rates. The ratio of those rate ratios is 0.00662/0.00631 = 1.05014 (95% CI: 0.07027, 15.69363), which is not significantly different from 1 (p=0.97171). However, in order to have enough precision to be 95% confident that the ratio (of rate ratios) is within the range $(0.80, 1.25)$, we would need to repeat this study 241 times (and each time having the same estimates of the ratio and its variance).

We cannot do similar analyses for the deaths, because the models will not converge because there are no deaths in any post-treatment months for the AP only and AP+PMQ$_{LD}$ groups.

3 Details on Quasi-Poisson Model

Because of the way the quasi-Poisson model is fit, the estimates are listed as log(f), where f are the factors expressed in the results section. Here are the results from the model fit.

```
Call:
glm(formula = cases ~ district + Month + AP.PMQ + AP + NoMDA +
    offset(log(pop)), family = quasipoisson(), data = dat)

Deviance Residuals:
     Min        1Q    Median        3Q       Max
-14.2043   -1.4124   -0.2298    1.3925   11.0850

Coefficients:
                    Estimate Std. Error t value Pr(>|t|)
(Intercept)         -5.98730    0.14901 -40.180  < 2e-16 ***
districtgradecomore  1.87072    0.14706  12.721  < 2e-16 ***
districtmiremani    -0.79974    0.25063  -3.191 0.002027 **
districtmutsamudu   -0.07642    0.20982  -0.364 0.716638
districtouani       -0.03102    0.22389  -0.139 0.890146
districtpomoni       0.70342    0.19397   3.626 0.000504 ***
districtsima         2.13322    0.16290  13.095  < 2e-16 ***
```

```
districttsembethou   0.71836    0.21299   3.373 0.001149 **
Month5              -0.02411    0.05095  -0.473 0.637363
Month6              -0.11033    0.05210  -2.118 0.037299 *
Month7              -0.23647    0.05391  -4.386 3.48e-05 ***
Month8              -0.24846    0.05409  -4.593 1.60e-05 ***
Month9              -0.12449    0.05229  -2.381 0.019659 *
AP.PMQ              -5.01728    1.19074  -4.214 6.55e-05 ***
AP                  -5.06621    0.69709  -7.268 2.16e-10 ***
NoMDA               -0.32543    0.03325  -9.786 2.52e-15 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for quasipoisson family taken to be 16.90248)

    Null deviance: 56908.3  on 95  degrees of freedom
Residual deviance:  1364.2  on 80  degrees of freedom
AIC: NA

Number of Fisher Scoring iterations: 5
```

To show the model fit, we give the observed incident rates (per 100,000) and the modeled incident rates. There is considerable lack-of-fit as can be seen by the overdispersion parameter (16.9). Here are the observed and the modeled rates:

	District	Month	year	cases	population	ObsRatePer100000	ModelRatePer100000
1	pomoni	4	2012	120	37629	318.9	507.3
2	pomoni	5	2012	139	37629	369.4	495.2
3	pomoni	6	2012	157	37629	417.2	454.3
4	pomoni	7	2012	153	37629	406.6	400.4
5	pomoni	8	2012	184	37629	489.0	395.7
6	pomoni	9	2012	264	37629	701.6	447.9
7	pomoni	4	2013	2	37629	5.3	3.4
8	pomoni	5	2013	0	37629	0.0	3.3
9	pomoni	6	2013	1	37629	2.7	3.0
10	pomoni	7	2013	0	37629	0.0	2.7
11	pomoni	8	2013	2	37629	5.3	2.6
12	pomoni	9	2013	1	37629	2.7	3.0
13	domoni	4	2012	236	59535	396.4	251.0
14	domoni	5	2012	122	59535	204.9	245.1
15	domoni	6	2012	158	59535	265.4	224.8
16	domoni	7	2012	123	59535	206.6	198.2
17	domoni	8	2012	119	59535	199.9	195.8
18	domoni	9	2012	37	59535	62.1	221.7
19	domoni	4	2013	1	59535	1.7	1.7
20	domoni	5	2013	2	59535	3.4	1.6
21	domoni	6	2013	2	59535	3.4	1.5

22	domoni	7	2013	1	59535	1.7	1.3
23	domoni	8	2013	0	59535	0.0	1.3
24	domoni	9	2013	0	59535	0.0	1.5
25	sima	4	2012	581	27795	2090.3	2119.3
26	sima	5	2012	439	27795	1579.4	2068.8
27	sima	6	2012	554	27795	1993.2	1897.9
28	sima	7	2012	571	27795	2054.3	1673.0
29	sima	8	2012	527	27795	1896.0	1653.1
30	sima	9	2012	468	27795	1683.8	1871.2
31	sima	4	2013	4	27795	14.4	13.4
32	sima	5	2013	2	27795	7.2	13.0
33	sima	6	2013	1	27795	3.6	12.0
34	sima	7	2013	3	27795	10.8	10.6
35	sima	8	2013	6	27795	21.6	10.4
36	sima	9	2013	0	27795	0.0	11.8
37	mutsamudu	4	2012	154	59388	259.3	232.6
38	mutsamudu	5	2012	102	59388	171.8	227.0
39	mutsamudu	6	2012	96	59388	161.6	208.3
40	mutsamudu	7	2012	80	59388	134.7	183.6
41	mutsamudu	8	2012	143	59388	240.8	181.4
42	mutsamudu	9	2012	157	59388	264.4	205.3
43	mutsamudu	4	2013	1	59388	1.7	1.5
44	mutsamudu	5	2013	2	59388	3.4	1.4
45	mutsamudu	6	2013	3	59388	5.1	1.3
46	mutsamudu	7	2013	2	59388	3.4	1.2
47	mutsamudu	8	2013	0	59388	0.0	1.1
48	mutsamudu	9	2013	0	59388	0.0	1.3
49	ouani	4	2012	134	44788	299.2	243.4
50	ouani	5	2012	69	44788	154.1	237.6
51	ouani	6	2012	84	44788	187.6	218.0
52	ouani	7	2012	76	44788	169.7	192.1
53	ouani	8	2012	91	44788	203.2	189.8
54	ouani	9	2012	128	44788	285.8	214.9
55	ouani	4	2013	0	44788	0.0	1.5
56	ouani	5	2013	0	44788	0.0	1.5
57	ouani	6	2013	1	44788	2.2	1.4
58	ouani	7	2013	0	44788	0.0	1.2
59	ouani	8	2013	0	44788	0.0	1.2
60	ouani	9	2013	1	44788	2.2	1.4
61	tsembethou	4	2012	150	25338	592.0	514.9
62	tsembethou	5	2012	112	25338	442.0	502.6
63	tsembethou	6	2012	146	25338	576.2	461.1
64	tsembethou	7	2012	106	25338	418.3	406.5
65	tsembethou	8	2012	87	25338	343.4	401.6
66	tsembethou	9	2012	94	25338	371.0	454.6
67	tsembethou	4	2013	4	25338	15.8	3.2

68	tsembethou	5	2013	0	25338	0.0	3.2
69	tsembethou	6	2013	0	25338	0.0	2.9
70	tsembethou	7	2013	0	25338	0.0	2.6
71	tsembethou	8	2013	0	25338	0.0	2.5
72	tsembethou	9	2013	0	25338	0.0	2.9
73	miremani	4	2012	50	67162	74.4	112.8
74	miremani	5	2012	60	67162	89.3	110.1
75	miremani	6	2012	72	67162	107.2	101.0
76	miremani	7	2012	81	67162	120.6	89.1
77	miremani	8	2012	80	67162	119.1	88.0
78	miremani	9	2012	58	67162	86.4	99.6
79	miremani	4	2013	0	67162	0.0	0.7
80	miremani	5	2013	1	67162	1.5	0.7
81	miremani	6	2013	4	67162	6.0	0.6
82	miremani	7	2013	0	67162	0.0	0.6
83	miremani	8	2013	0	67162	0.0	0.6
84	miremani	9	2013	0	67162	0.0	0.6
85	gradecomore	4	2012	6001	420000	1428.8	1630.0
86	gradecomore	5	2012	6220	420000	1481.0	1591.2
87	gradecomore	6	2012	5978	420000	1423.3	1459.7
88	gradecomore	7	2012	6160	420000	1466.7	1286.8
89	gradecomore	8	2012	5799	420000	1380.7	1271.4
90	gradecomore	9	2012	6291	420000	1497.9	1439.2
91	gradecomore	4	2013	5744	420000	1367.6	1177.2
92	gradecomore	5	2013	5598	420000	1332.9	1149.2
93	gradecomore	6	2013	4548	420000	1082.9	1054.2
94	gradecomore	7	2013	3050	420000	726.2	929.3
95	gradecomore	8	2013	3244	420000	772.4	918.2
96	gradecomore	9	2013	4140	420000	985.7	1039.4

4 Tests for Table 2

Table 2 gives P. falciparum K13 sequence polymorphisms on Anjouan Island. To test for changes from before MDA to after MDA, we use a Fisher's exact test (two-sided, Fisher-Irwin version). The p-values for each mutation are:

Y500Y	N531N	D464H	S477Y	N490H	V520A	N554H	A578S
0.1946	1.0000	0.6394	0.2097	1.0000	0.2097	1.0000	1.0000

References

1. Jefferson, T, Rivetti, D, Rittetti, A, Rubin, M, DiPrietrantonj, C, Demicheli, V. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. Lancet 2005; 366: 1165-74.