Ann Natl Acad Med Sci (India), **43(2):** 65-74, 2007

Infectious Diseases Control : From Product Development to Public Health

Dr. (Mrs.) N.A. Kshirsagar
Director (ME & H), Prof. & Head,
Department of Clinical Pharmacology,
Seth G.S. Medical College & KEM Hospital, Parel, Mumbai- 400 012, India

Summary

There are difficulties in controlling environment conditions and preventing vector breeding and propagation. New drugs, drug combinations and regimens and vaccines need to be developed and tested. However, it is also of great importance to note that concerted efforts of various healthcare workers from different disciplines and administrations are needed to control tropical diseases.

Key words: Leptospirosis, malaria, leishmaniasis , filariasis.

In this paper, I will share my experiences at the Seth G.S. Medical and KEM Hospital as Clinical Pharmacologist and as an administrator for control of infectious diseases.

Seth G.S. Medical College and KEM Hospital teaching hospital under the Municipal Corporation of Greater Mumbai (MCGM) is an 1800 bedded tertiary care hospital with an annual OPD attendance of 15.0Lakh, Indoor admission of 80000 and surgeries over 60,000 and 8000 deliveries. In the year 2000, state of art emergency services section was established at a total cost of Rs.2.0 crores with funding from a donor and MCGM.

In the year 2005, on 26th July, Mumbai had a rainfall of 944mm in 4 hours, this coupled with high tide, flooding of river, gushing of water through the city, water logging and home bound office goers, resulted in a disaster. There were house collapses and deaths due to drowning. There was fear of epidemics of water borne and vector borne diseases. The entire machinery of health

Correspondence: *Dr. (Mrs.) N.A. Kshirsagar,* Director (ME & H), Prof. & Head, Department of Clinical Pharmacology, Seth G.S. Medical College & KEM Hospital, Parel, Mumbai- 400 012. INDIA. Glaxo Oration 2005-2006 , delivered at Annual Meeting at Hyderabad, 2006.

department of MCGM was put in action. At the KEM Hospital, a fever casualty was set up, the emergency services laboratory was provided with extra manpower. The Preventive and Social Medicine (PSM) department launched a massive door to door visit and door step camp programme. Over 1 month 107 doctors treated 1.5 lakh patients. In comparison to other cities in the world, faced with similar flood situation, our various strategies helped in containing the impact of disaster on health. The number of leptospirosis cases and mortality in comparison to pre flood years increased but not as badly in similar situation in other towns e.g. Rio de Janeiro (Table 1) (1).

Table 1

Impact of Community services

Leptospirosis morbidity and mortality data

Population(Lakhs)	Incidence (per lakh)	Case fatality rate (per 100)
	Mumbai	
	Year 2004	
38.8	2.1	7.3
	Year 2005	
39.49	7.85	8.7
	Rio de janeiro floods in 1996	
	Previous years	
2.75	1	20 estimated
	Flood year	
2.75	26.8	Not Available

(In press) Kshirsagar et al, JPGM, Oct 2006

Malaria had been on the rise in the city of Mumbai since the 1990's (Figure 1). Control of malaria in Mumbai actually was well managed till 1990. It was recognized since 1920's that anopheles stephensi vector for malaria breeds in fresh water. As such the Municipal Corporation has a statutory requirement of mosquito proofing of fresh water tanks such as overhead water storage tanks. The design of water tank that ensures mosquito proofing is stipulated. With this simple measure, mosquito breeding and malaria could be contained till 1990's. However, with multiple high rise buildings, construction work and immigrants, anopheles stephensi's breeding and cases of malaria increased.

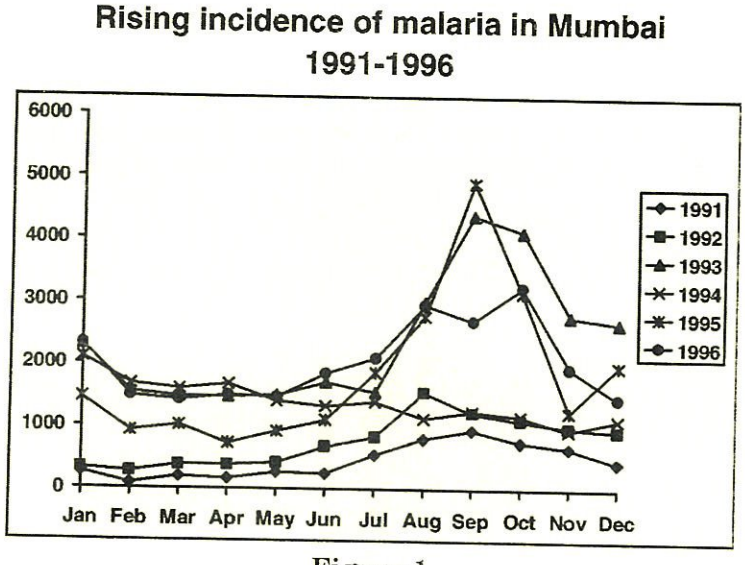

Figure 1

Other important reason for increase in malaria was drug resistance and inadequate, inappropriate treatment. Our studies carried out in 1993 showed that efficacy of single dose chloroquine, given as presumptive treatment, had declined (2) (Figure 2). Studies in subsequent years demonstrated non response to full dose of chloroquine. 30-50% cases were noted to be chloroquine resistant (3) (Figure 3). Non response to chloroquine in patient could be due to variety of reasons, such

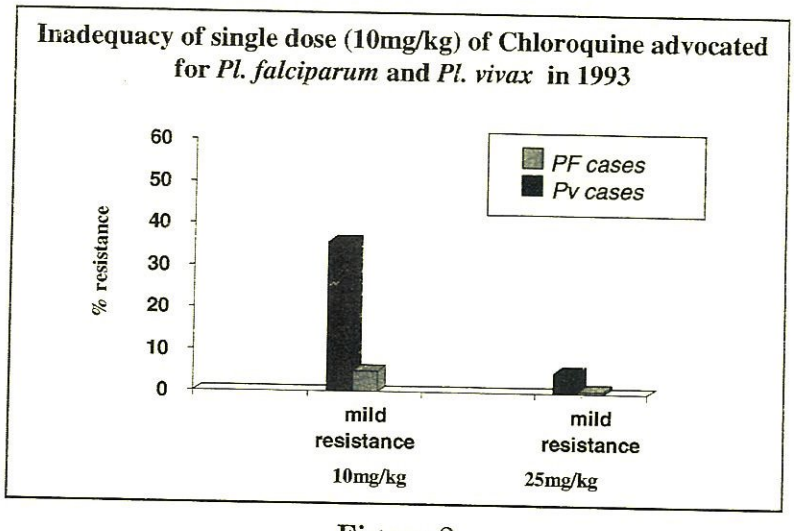

Figure 2

as substandard drug, poor absorption. In vitro resistance testing was done using WHO micro test kit. Blood from patient is incubated over 18 hours in a microtitre plate pre dosed with different concentrations of antimalarials. If the strain is resistant, formation of schizonts will take place. Our in vitro studies showed chloroquine resistance (4) (Figure 4). Our subsequent studies showed

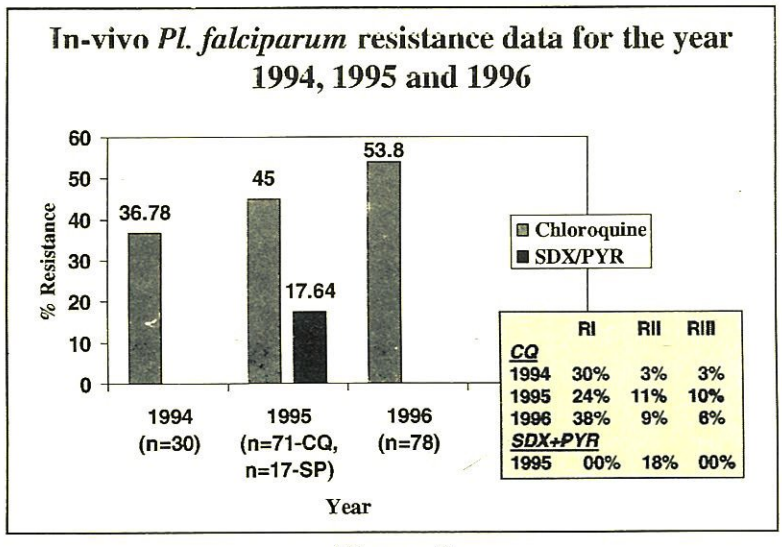

Figure 3

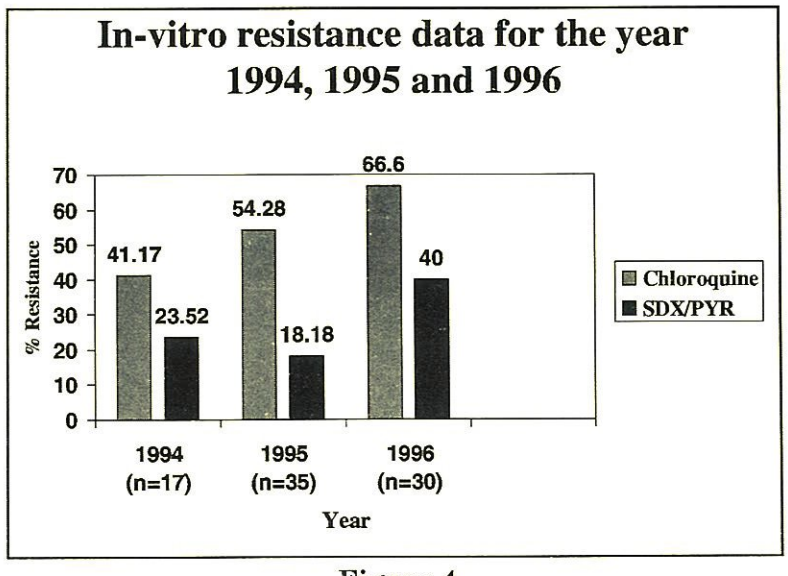

Figure 4

resistance to Sulphadoxine + Pyrimethamine (SDX+PYR) as well. (3,4) (Figure 3).

Artemisinin derivatives, which have been introduced, have the advantage of quick onset of action as well as greater efficacy in reducing parasite burden. However, the duration of action is short. Hence these drugs need to be given for 5-7 days or given for 3 days in combination with long acting drugs. Artemisinins have the advantage of acting on gametocyte thus reducing transmission. Unlike P. vivax, P. falciparum gametocytes are not acted on by antimalarials used for clinical attack. Primaquine has gametocytocidal action and is used as single dose (45mg) for P. falciparum. Our studies in Mumbai showed that over 25% patients had gametocytes on admission. Without Primaquine, patients treated with CQ or CQ+SP (parasites sensitive to CQ or CQ + SP) had viable gametocytes upto day 29. The data on gametocyte prevalence after different schizonticidal drugs and priqmuine in drug sensitive cases of uncomplicated malaria is shown in Figure 5 (5). Treatment with single dose of 45mg PQ, given on day 4, reduced prevalence of gametocytes by approximately 70% (6).

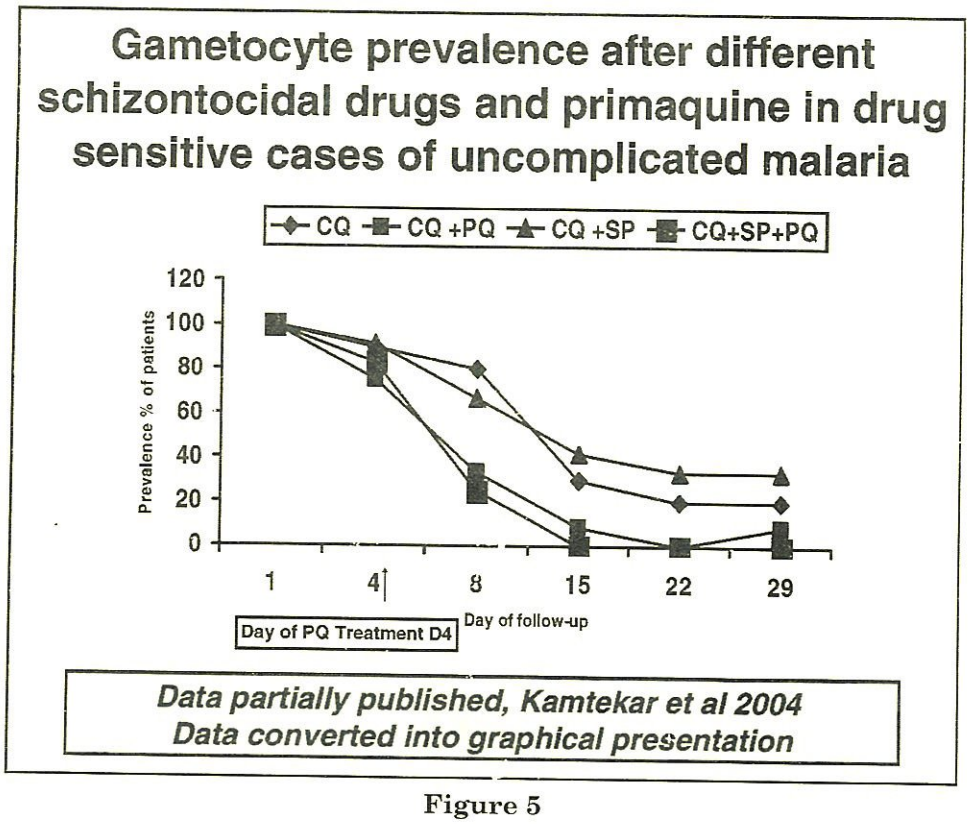

Figure 5

Bulaquie is new drug (formerly called CDRI 80/60)developed by Central Drug Research Institute (CDRI), Lucknow, India, marketed by Nicholas Piramal (7).

In a study comparing gametocytocidal effect of BQ (single,75mg dose) vs PQ (single, 45mg dose), in uncomplicated falciparum malaria patients receiving combination of Quinine (30mg/kg.day) + Doxycycline (100g/kg.day) x7days , of the patients who received PQ (single, 45mg dose on day 4) 77% were found gametocytaemic on Day 8, while patients receiving BQ (single, 75mg dose on day 4) 11% was found gametocytaemic on Day 8 (8).

The current ongoing study comparing higher dose of PQ (single dose 60mg) with that of BQ (single dose 75mg) and standard 45 mg PQ dose, given on day 4, has shown that the prevalence of gametocytemia reduced by 90% in both uncomplicated and

severe malaria on day 8 in two of the groups treated with 75mg BQ and 60mg PQ while with 45mgprimaquine, it reduced by 55% (unpublished data) (Figure 6).

Thus, present recommendation of 45 mg primaquine is only 50-70% effective, there is need to review the policy.

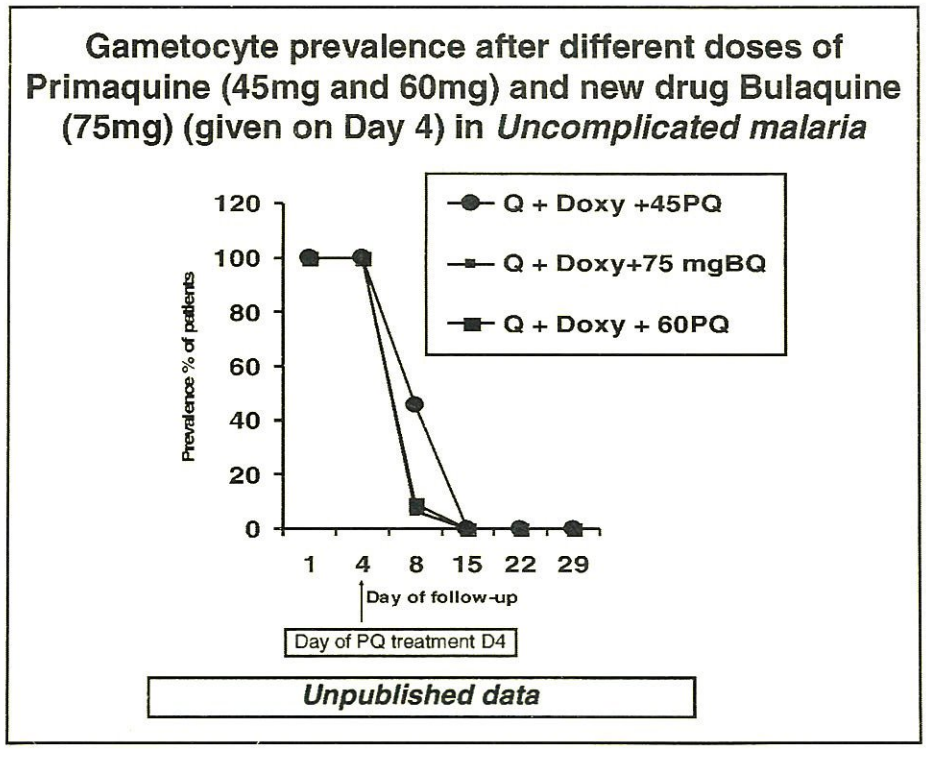

Figure 6

Primaquine is also used for preventing relapses in P.vivax cases World Health Organization (WHO) recommends primaquine treatment with 15 mg daily for 14 days. In India, based on studies done in 1977, primaquine treatment for 5 days was advocated in National Programme. However, we observed in Mumbai that 5 day regimen was as bad as placebo (7) (Table 2). Our subsequent studies showed that there were recurrences even after 14 days treatment. In order to differentiate between reinfection and relapse, we carried out genotyping using Polymerase Chain Reaction (PCR) - Single strand Conformational Polymorphism (SSCP). The PCR-SSCP analysis showed that 60% of recurrences are relapses and 40% are reinfection (9) (Table 3). Increasing dose and duration of Primaquine to 30mg for 14days is useful however, recurrences as well as relapses are noted even after these

Table 2

Evaluation of efficacy of 5 and 14 days Primaquine therapy versus placebo

	A	B	C
	No Primaquine	15mgX5days	15mgx14days
Evaluable	60	62	63
Recurrences			
Month 1	2	2	0
Month2	1	5	0
Month3	3	3	0
Month4	1	3	0
Month5	0	2	0
Month 6	0	1	0
Total	7 (11.7%)	16 (26.7%)	0(0%)

Table 3

Evaluation of efficacy of 14d primaquine treatment for *Plasmodium vivax:* PCR - SSCP analysis of paired primary and relapse isolates

Mth	No primaquine (n = 101, evaluable)	Recurrences	14d primaquine (n=103, evaluable)	Recurrences	PCR - SSCP results (only for 14 day PQ group)
1	138	1	123	0	NA
2	136	4	121	2	1 true relapse 1 did not amplify
3	120	4	118	3	1 true relapse 2 re-infections
4	111	1	116	0	NA
5	105	1	111	1	true relapse
6	101	2	103	0	NA
Total	101	13(12%)	103	6(5.8%)	3/5 (60%) 3 true relapses

regimens (unpublished data). (Table 4) We have carried out Primaquine levels to ensure adequate Primaquine concentration. There is urgent need for new drug/substitute for Primaquine. Bulaquine, developed by Central Drug Research Institute (CDRI) Lucknow, is an alternative. Our studies have shown that it is effective in P. falciparum as gametocytocidal, however, its antirelapse efficacy at different doses needs to be investigated.

The International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi, has developed a new vaccine. The vaccine is a recombinant fusion protein, a component of P. vivax duffy binding protein and is expected to prevent RBC invasion by P. vivax.

Leishmaniasis and filariasis are other tropical diseases, which are vector borne (sandfly and culex mosquito respectively) and potentially preventable . However, control of environment requires concerted efforts. Using Pharmacological tools to prevent spread and thus eliminate the disease when the disease affects only human, has been an important strategy followed. For filariasis, using yearly Mass Drug Administration (MDA) in infected areas has been recommended. Diethylcarbamazine (DEC) combined with Albendazole (ALB) has been shown to decrease microfilaremia to levels that could break transmission. Our studies in Wardha District of Maharashtra, has shown that DEC alone is as effective as DEC+ALB (unpublished data) (Table 5).

Table 4

Recurrences in parasitemia in each group along with drop outs in Various Primaquine Regimens given as Antirelapse

	Treatment group			
	A No PQ	B 15mg/d x 14 days	C 30mg/d x 7 days	D 30mg/d x 14 days
No. of patients enrolled	397	398	381	380
Completed 12 months f/up	305 (76.8%)	322 (80.9%)	298 (78.3%)	234 (58%)
Total recurrences of parasitemia	58 (14.6%)	24 (6.03%)	30 (7.87%)	27 (7.1%)
Drop outs	92 (23.2%)	76 (19.1%)	83 (21%)	63 (21%)
Drop outs due to AE	None	1/76 (1.3%)	1/83 (1.2%)	7/63 (11.1%)

For Leishmaniasis, due to development of resistance to standard treatment (antimonials) various alternative treatments have been developed. Amphotericin B is an effective drug. However, it produces serious infusion related toxicity (chills and rigors), hypokalemia and Nephrotoxicity. We developed in collaboration with Dr. Bacchawat, Delhi University, liposomal amphotericin which is useful for fungal infection and Leishmaniasis and is now marketted . Our studies have shown its efficacy is 100% at 2mglkg dose given for 10 days (10) (Table 6).

Table 5

Efficacy and tolerability of re-treatment with single doses of Diethylcarbamazine (DEC) and Diethylcarbamazine plus Albendazole (ALB) for two consecutive years in a field study in lymphatic filariasis in India

	A (DEC + Placebo ALB)				B (DEC + Active ALB)			
	0 months Oct 2000	12 months Nov 2001	24 months Nov 2002	36 months Nov 2003	0 months Oct 2000	12 months Nov 2001	24 months Nov 2002	36 months Nov 2003
Mf - PS	69 (100%)	15 (21.7%)	4 (5.7%)	2 (2.8%)	70 (100%)	14 (20%)	1 (1.4%)	2 (2.8%)
Mf-NP	Not Done	24 (100%)	15 (62.5%)	8 (33.3%)	Not done	29 (100%)	16 (55.1%)	4 (13.7%)
ICT	Not Done	44 (100%)	45 (>100%)	37 (84%)	Not Done	47 (100%)	54 (>100%)	42 (89%)

Table 6

L-AMP-LRC-1 in leishmaniasis Dose searching studies freshly diagnosed cases of leishmaniasis

Dose Schedule	Enrolled	Responded to assigned schedule (%)	No. of extra doses for complete cure (no.of cases)
1.0 mg/kg daily x 21	15 (+1)[a]	14 (93.3%)	14 (1)
2.0 mg/kg daily x 10	5	5 (100%)	0
3.0 mg/kg daily x 7	5	4 (80%)	3 (1)
3.0 mg/kg daily x 5	11	10 (90.9%)	4 (1)
2.0 mg/kg daily x 7	6	4 (66.7%)	10 (1) & 3 (1)
Total	42	37	5

[a]- one patient in this dosage group died after receiving 4 doses and is therefore non-assessable.

There are difficulties in controlling environment conditions and preventing vector breeding and propagation. New drugs, drug combinations and regimens and vaccines need to be developed and tested. However, it is also of great importance to note that in concerted efforts of various healthcare workers from different disciplines and administrations are needed to control tropical diseases.

References

1. Kshirsagar NA, Shinde, Mehta S, Chaudhary S. (Oct 2006). Floods in Mumbai- impact of Public health service by hospital Staff and Medical Students. JAPI (in press).
2. Potkar CN, Kshirsagar NA, Kathuria R. (1995). Resurgence of malaria and drug resistance in plasmodium falciparum and plasmodium vivax species in Bombay. *JAPI.* **43**: 336-338.
3. Garg MR, Gogtay NJ, Kshirsagar NA. (1996). Efficacy of sulfadoxine pyrimethamine in chloroquine resistant falciparum malaria in Bombay. *JAPI.* **44(10)**: 683-685.
4. Garg MR, Gogtay NJ, Kotwani RN, Bodhe PV, Kshirsagar NA. (1999). Resurgence of malaria in Mumbai – Is escalating chloroquine resistance a cause? *JAPI.* **47:** 377-379.
5. Kamtekar KD, Gogtay NJ, Dalvi SS, Karnad DR, Chogle AR, Aigal U, Kshirsagar NA. (2004). A prospective study evaluating the efficacy of a single 45mg dose of primaquine as a gametocytocidal agent in patients with Plasmodium falciparum malaria in Mumbai, India. *Annals of Tropical Medicine and Parasitology.* **98**: 453-8.
6. Gogtay NJ, Chogle AR, Sorabjee JS, Marathe SN, Kshirsagar NA. (1999). Poor gametocytocidal activity of 45 mg primaquine in chloroquine-treated patients with acute, uncomplicated, Plasmodium falciparum malaria in Mumbai (Bombay): an issue of public-health importance. *Ann of Trop Med & Parasitology.* **93:** 813 – 816.
7. Dutta GP, Puri SK, Bhaduri (1989). Radical curative activity of a new 8-aminoquinolone derivative (CDRI 80/53) agaist plasmodium cynomolgi B in monkeys. *Am J Trop Med Hyg.* **41:** 635-636.
8. Gogtay NJ, Kamtekar KD, Dalvi SS, Chogle AR, Aigal U, Kshirsagar NA. (2004). Preliminary report of the evaluation of the gametocytocidal action of bulaquine in adult patients with acute Plasmodium falciparum malaria. *Annals of Tropical Medicine and Parasitology.* **98:** 525-8.
9. Rajgor DD, Gogtay NJ, Kadam VS, Kamtekar KD, Dalvi SS, Chogle AR, Aigal U, Bichile LS, Kain KC and Kshirsagar NA.(2003). Efficacy of 14 day primaquine regimen in preventing relapses in patients with *Plasmodium vivax* malaria in Mumbai, India. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* **97**: 438-440.
10. Bodhe PV, Kotwani RN, Kirodian BG, Pathare AV, Pandey AK, Thakur CP, Kshirsagar NA.(1999). Dose ranging studies on liposomal amphotericin B (L-AMP- LRC-1) in the treatment of visceral leishmaniasis. *Trans Roy Soc Trop Med Hyg.* **93**: 314–318.