

1 Slow Release Ivermectin Formulation for Malaria Control: a Pilot Study in 80-kg Pigs

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14 Vector control with long-lasting insecticidal nets (LLINs) and indoor residual spraying are
15 responsible for more than two thirds of the reduction seen in malaria prevalence in Africa
16 over the last 15 years (1). Yet the behavioral plasticity of mosquito vectors can lead to
17 residual transmission and possibly hamper elimination efforts (2, 3).

18 One identified source of residual transmission is partial zoophagy. Mosquitoes that feed on
19 peridomestic livestock can avoid contact with insecticides and survive to continue
20 transmission once human blood is available again (3). This behavioral pattern could be seen
21 after the scale-up of LLINs that put selective pressure on vectors that bite predominantly
22 humans indoors (4), either by allowing a shift to a vector species with different behavior (5)
23 or by selecting members of the same species that circumvent LLINs by biting outdoors (6) or
24 outside sleeping hours (7).

25 Ivermectin is an endectocide, a drug that kills ectoparasites that feed on treated subjects.
26 Ivermectin mass drug administration to humans has been proposed as a potential
27 complementary measure to reduce malaria transmission (8). Additional treatment of
28 peridomestic livestock with ivermectin could reduce malaria transmission by killing partially
29 zoophagic vectors (9) and also contribute to human wellbeing via the one-health concept,
30 improving food production and economic benefits of animal owners (10).

31 Ivermectin, however, has a relatively short half-life (3.5 days in pigs (11) and 2.8 days in
32 cattle (12)), although veterinary use allows more flexibility in dose and route of
33 administration. Even novel injectable formulations at 3.15% used at a three-fold dose would
34 only sustain mosquito-killing concentrations for maximum estimated 40 days in cattle (13).
35 Consideration should be given to longer-lasting formulations specifically conceived for
36 vector control.

37 We previously showed that subcutaneous long-lasting formulations sustained mosquito-
38 killing ivermectin levels in a rabbit model for more than six months (14). Using the same
39 formulations, we aimed at achieving stable and safe ivermectin levels in a larger mammal,
40 the pig.

41 **Methods.** We chose two 80-kg hybrid mini pigs to facilitate extrapolation to larger
42 livestock such as cattle. We tested the two formulations of subcutaneous silicone rods that
43 showed the most promising pharmacokinetic profile in our previous experiment (14). The
44 rods are 40 mm long and have a 1 mm radius; four or five devices are inserted
45 subcutaneously in the back or thighs by means of a trocar used for commercially available
46 hormonal implants. Formulation “F” contains 80% ivermectin (29 mg), 7% sucrose and 13%
47 deoxycholate. Formulation “X” contains 35% ivermectin (13 mg), 10% sucrose and 55%

48 deoxycholate, which greatly increases the elution of the drug (for further details on implant
49 design refer to (14)).

50 Plasma ivermectin levels were measured weekly for 12 weeks after the first month. At
51 completion of the experiment, the implants were removed and the ivermectin remaining in
52 the rods quantified. Animals were checked daily for toxicity. The protocol was approved by
53 the Institutional Animal Care and Use Committee of the University of Navarra.

54 **Results.** The implants sustained stable ivermectin plasma levels around 20 ng/ml for
55 more than 12 weeks (Figure 1), greatly exceeding 6 ng/ml, the concentration needed to kill
56 50% of *Anopheles gambiae* mosquitoes in 10 days (15). Both formulations showed a similar
57 pharmacokinetic pattern, formulation “F” eluted 47% of its ivermectin content while
58 formulation “X” eluted 55%. The mean daily dose received by the pig with formulation “F”
59 was 43 mcg/kg/day and for that with formulation “F” 9.8 mcg/kg/day. No clinical adverse
60 effects were seen in the pigs.

61 **Conclusion.** Our results show there is potential to safely sustain mosquitocidal levels
62 of ivermectin in larger mammals for months using a subcutaneous formulation. Whether an
63 entomologically relevant outcome can be expected should be tested by means of a cluster
64 randomized trial. This approach could contribute to human wellbeing not only by reducing
65 residual malaria transmission driven by zoophagic vectors but also by improving the health
66 of economically relevant livestock. Hence this intervention could be attractive for livestock
67 owners, possibly opening the door for previously unforeseen funding collaborations.

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70 We declare no competing interests.

71

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Legend

FIG. 1. Ivermectin plasma levels after implantation of a slow release formulation in two 80 kg-pigs. Levels above the 10-day lethal concentration 50 for *An. gambiae* (double blue line) are sustained for at least 12 weeks. We expect this effect to last for at least 6 months given that the implants still contained 45-53% of ivermectin after removal at 12 weeks. The dotted lines are included for comparison; red reflects the approximate PK of a single subcutaneous 300 mcg/kg dose of 1% ivermectin in pigs (11), orange reflects the approximate PK of a single subcutaneous 630 mcg/kg dose of 3.15% ivermectin in cattle (13).

