

Table of Contents

<i>Preface</i>	<i>i</i>
<i>Table of Contents</i>	<i>iii</i>
<i>List of tables</i>	<i>vi</i>
<i>List of figures</i>	<i>vii</i>
<i>List of abbreviations</i>	<i>viii</i>
<i>Acknowledgments</i>	<i>xii</i>
<i>Summary</i>	<i>xvi</i>
<i>Chapter One</i>	<i>1</i>
1. <i>Introduction</i>	2
1.1 The Global and African burden of malaria	2
1.2 The Global effort to control malaria	3
1.3 Amodiaquine for the treatment of malaria	6
1.4 Artemisinin and Naphthoquine (ARCO) for the treatment of malaria	7
1.5 Dosing in children	8
1.6 Issues concerning the current dose recommendation in children	10
1.7 Modelling and simulation in aiding dose regimen selection in children	11
1.8 Objectives and outline	13
1.9 References	14
<i>Chapter Two</i>	20
2. <i>Methodology</i>	21
2.1 Clinical studies and data	21
2.1.1 Amodiaquine study (Chapters 3 & 4)	21
2.1.2 Artemisinin Naphthoquine (ARCO) study (Chapter 5)	21
2.2 Study area and study subjects	22
2.2.1 Amodiaquine study (Chapters 3 & 4)	22
2.2.2 Artemisinin Naphthoquine study (Chapter 5)	22
2.3 Methods	23
2.3.1 Amodiaquine study (Chapter 3 & 4)	23
2.3.2 Artemisinin Naphthoquine study (Chapter 5)	23
2.3.3 Modelling pharmacokinetic data	23
2.3.4 Data analysis and pharmacokinetic modeling	28
2.3.5 Model evaluation	32
2.3.6 Simulation	33

2.4	Ethics.....	34
2.5	References	36
<i>Chapter Three.....</i>		<i>40</i>
<i>3. Article: Population Pharmacokinetics of the Antimalarial Amodiaquine: A Pooled Analysis to Optimize Dosing.....</i>		
3.1	Abstract.....	42
3.2	Introduction	43
3.3	Results.....	45
3.4	Discussion.....	60
3.5	Materials and methods.....	66
3.6	Supplementary material	73
3.7	Acknowledgements.....	76
3.8	Contribution information.....	77
3.9	References	78
<i>Chapter four.....</i>		<i>84</i>
<i>4. Population pharmacokinetics properties of amodiaquine in Ghanaian children and adults with uncomplicated falciparum malaria using capillary whole blood samples.....</i>		
4.1	Abstract.....	85
4.2	Introduction	86
4.3	Methods.....	87
4.4	Results.....	89
4.5	Discussion and conclusion	94
4.6	Acknowledgments.....	97
4.7	References	98
<i>Chapter five.....</i>		<i>101</i>
<i>5. Population pharmacokinetics of antimalarial Naphthoquine in combination with Artemisinin in Tanzanian children and adults.....</i>		
5.1	Abstract.....	102
5.2	Introduction	103
5.3	Methods.....	104
5.4	Results.....	108
5.5	Discussion.....	112
5.6	Acknowledgements.....	115

5.7	Appendix	116
5.8	References	121
<i>Chapter six.....</i>		<i>126</i>
<i>6. Overall discussion and conclusions.....</i>		
6.1	Main findings	128
6.1.1	Amodiaquine kinetics (Chapter 3 & 4)	128
6.1.2	Venous plasma concentration (Chapter 3).....	128
6.1.3	Capillary whole blood concentration (Chapter 4)	128
6.1.4	Comparison of amodiaquine kinetics in this thesis	129
6.1.5	Amodiaquine covariates (Chapter 3 & 4)	129
6.1.6	Naphthoquine kinetics (Chapter 5)	132
6.1.7	Naphthoquine covariates (Chapter 5)	132
6.1.8	Simulation.....	133
6.2	Implication for future research.....	137
6.3	Implication for new malaria drugs in development.....	140
6.4	Implication for policy and practice.....	140
6.5	General conclusions.....	145
6.6	References	147
<i>7. Personal remarks</i>		<i>154</i>
<i>8. Curriculum vitae.....</i>		<i>155</i>