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Summary

Background: The neglected tropical diseases (NTDs) comprise of a group of infections, that primarily occur in impoverished communities and may impair the course and outcome of pregnancy, childhood growth, intellectual development, education and worker productivity. Long-term chronic infection may result in disfigurement and stigmatization. Hence, the NTDs may exacerbate poverty, but because there are only limited commercial opportunities, the fight against these conditions has been widely neglected. Amongst others, helminth infections such as schistosomiasis (e.g., due to *Schistosoma haematobium* and *S. mansoni*), soil-transmitted helminthiasis (e.g., due to *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm) and food-borne trematodiasis (e.g., due to *Clonorchis sinensis*, *Opisthorchis viverrini*, *Fasciola* spp. and *Paragonimus* spp.) belong to the NTDs.

For better quantifying the health burden caused by diseases, injuries and risk factors, in the 1990s, the World Health Organization (WHO) and the World Bank developed the disability-adjusted life year (DALY) metrics, as a scalable, time-based measure. DALYs combine years of life lost and years lived with disability in a single metrics and should help to better prioritize public health activities. In 2007, a comprehensive revision of all global burden estimates was launched, which also aimed at the inclusion of not yet assessed conditions such as food-borne trematodiasis.

The increasing popularity of DALYs and burden of disease estimates sparked also renewed interest in the underlying epidemiological parameters. For instance, it became clear that for the NTDs, which mainly cause morbidity rather than mortality, the assessment of the average disability incurred by a diseased individual is crucial for correctly compiling data to global burden estimates. Interestingly, anamnestic questionnaires to assess morbidity due to helminth infections had been used before in attempts to better gauge helminth control efforts.

Goal and specific objectives: The overarching goal of this PhD thesis was to develop, validate, and apply tools for assessing the morbidity and burden caused by NTDs at different geographical scales. The following three specific objectives were pursued in order to achieve this goal. First, to participate in the global burden of diseases, injuries and risk factors study 2010 and assess – for the first time – the global burden of food-borne trematodiasis. Second, to generate new evidence on the disability incurred by individuals infected with schistosomes and/or soil-transmitted helminths in field-based epidemiological investigations in rural Côte d'Ivoire and compare the results with the most recent disability weights of the global burden of disease study. Third, to explore the potential of simple and low-cost anamnestic

questionnaire tools for the assessment of morbidity due to schistosomiasis and soil-transmitted helminthiasis in the recently established Taabo health demographic surveillance site (Taabo HDSS) in Côte d'Ivoire in order to identify high-risk groups and guide control measures.

Methods: To tackle the first objective, a systematic review was conducted and the current knowledge about the manifestation, diagnosis, management and epidemiology of food-borne trematodiasis summarized. The global burden of food-borne trematodiasis was then assessed according to the latest global burden of diseases study guidelines.

Regarding the second objective, a first cross-sectional survey was carried out with 156 schoolchildren in south Côte d'Ivoire in early 2010. Children were parasitologically tested for helminth and *Plasmodium* spp. infections, clinically examined, interviewed with a quality of life questionnaire and invited to participate in a maximal multistage 20 m shuttle run test. A second cross-sectional survey was conducted in the recently established Taabo HDSS in south-central Côte d'Ivoire in mid-2010. Overall, 187 adults were parasitologically tested for helminth and *Plasmodium* spp. infections and interviewed with a quality of life questionnaire. In the analysis of each survey, the different test results were juxtaposed to each other.

For the third objective, 187 adults participating in the second annual parasitological surveys of the Taabo HDSS in 2010, and 146 children and 439 adults participating in the third annual parasitological survey in 2011 were interviewed with anamnestic questionnaires. The questionnaires contained questions about risk factors, signs and symptoms that are often associated with schistosomiasis and soil-transmitted helminthiasis. The questionnaire results were compared with the participants' parasitological results in order to evaluate the diagnostic properties (sensitivity, specificity, positive and negative predictive values) of single responses and response combinations.

Results: The estimates on the global burden of human food-borne trematodiasis indicate that 56.2 million people were infected with food-borne trematodes worldwide in 2005, 7.9 million suffered from severe sequelae and 7,158 died due to cholangiocarcinoma and cerebral infection. These figures result in a global burden of 665,352 DALYs for the year 2005.

With regard to individuals' disability measurements, no effect of schistosomiasis and soil-transmitted helminthiasis on schoolchildren's physical fitness could be identified, irrespective of whether objectively measured shuttle run test results or questionnaire results on self-reported physical fitness were considered. However, statistically significant correlations between the children's shuttle run test and questionnaire results were found. In the second

survey, adults infected with *S. mansoni* or *T. trichiura* reported a significantly lower quality of life (-16.4%; p = 0.011 and -12.6%; p = 0.035, respectively).

The results on specificity, sensitivity, positive and negative predictive values of the risk factors, signs and symptoms considered in the anamnestic questionnaire in the 2010 study revealed neither a promising diagnostic single indicator nor an appropriate combination. In-depth analyses of data collected during the larger survey done in 2011 are underway.

Conclusions: Despite disclosing many unsolved issues about the global burden of disease concept, knowledge gaps about food-borne trematodiasis and deliberately making conservative estimates, the identified disease burden reveals food-borne trematodiasis as an important cluster of neglected diseases. Particularly in the most endemic areas, efforts to control human food-borne trematodiases are essential.

The results on individuals' disability incurred by schistosomiasis and soil-transmitted helminthiasis are ambiguous. However, the significant correlation between objectively measured and self-reported physical fitness of schoolchildren is a promising indication for the more general use of quality of life questionnaires. Indeed, the figures on adults' reduced quality of life indicate a stronger negative effect of these parasitic infections than currently assumed in most burden of disease compilations. The need for further innovation, validation and application of systematic, truly interdisciplinary, field-based, epidemiological approaches to gather additional evidence has been emphasized and a potential way forward outlined.

As the whole project on the potential of further refined anamnestic questionnaires to guide schistosomiasis and soil-transmitted helminthiasis control efforts is still in an early exploration phase, findings presented in this PhD thesis are rather suggestive and should be interpreted with caution. Of note, if it may become possible to elicit effects of NTDs with carefully adapted and applied quality of life questionnaires, it is conceivable that disease-associated risk factors, signs and symptoms allow for the development of anamnestic questionnaires. The potential benefits of such anamnestic questionnaire tools warrant further efforts, optimally within the frame of more comprehensive research collaborations aiming at the elaboration of integrative diagnosis and treatment algorithms. Detailed suggestions for future studies have been provided.

Zusammenfassung

Hintergrund: Die sogenannten vernachlässigten Tropenkrankheiten bestehen aus einer Gruppe von Infektionen, die vor allem in verarmten Gemeinschaften hoch endemisch sind, und können das Wachstum von Kindern, die intellektuelle Entwicklung, die schulische Leistung und die Arbeitsproduktivität beeinträchtigen. Zudem können sie zu Entstellungen und Stigmatisierung führen. Folglich sind auch die vernachlässigten Tropenkrankheiten selbst armutsfördernd, aber weil kommerziellen Möglichkeiten zu deren Bekämpfung sehr beschränkt sind, wurden sie bisher weitestgehend nicht beachtet. Nebst anderen Krankheiten, gehören Infektionen mit Würmern der Spezies *Schistosoma haematobium*, *S. mansoni*, *Ascaris lumbricoides*, *Trichuris trichiura*, Hakenwürmer (*Ancylostoma duodenale* und *Necator americanus*) und durch Nahrungsmittel übertragene Trematodeninfektionen zu den vernachlässigten Tropenkrankheiten.

Um die durch Krankheiten, Verletzungen und Risikofaktoren verursachte Krankheitslast besser zu bemessen, entwickelte die Weltgesundheitsorganisation (WHO) zusammen mit der Weltbank gegen Ende des 20. Jahrhunderts die sogenannten „behinderungsbereinigten Lebensjahre“ (disability-adjusted life years; DALYs) als eine neue, skalierbare, zeitbasierte Masseinheit. Diese DALYs kombinieren verlorene Lebensjahre aufgrund eines vorzeitigen Todes mit Lebensjahren gelebt mit einer Beeinträchtigung in einer einzigen Zahl, was der besseren Prioritätensetzung im Gesundheitswesen helfen soll. Im Jahr 2007 wurde eine komplette und systematische Revision von allen Schätzungen zu globalen Krankheitslasten lanciert. Diese Revision soll auch bisher noch nicht erfasste Krankheiten, wie zum Beispiel durch Nahrungsmittel übertragene Trematodeninfektionen, berücksichtigen.

Die zunehmende Popularität von den DALYs und Schätzungen zur Krankheitslast hat auch das Interesse an den zu Grunde liegenden epidemiologischen Parametern neu entfacht. Zum Beispiel wurde erkannt, dass im Fall der vernachlässigten Tropenkrankheiten, welche vor allem zu Morbidität und nicht Mortalität führen, die Erfassung der durchschnittlichen Beeinträchtigung eines Patienten entscheidend ist um die geschätzte Krankheitslast korrekte aufsummieren zu können. Interessanterweise wurden anamnestische Fragebogen zur Erfassung der durch Wurmerkrankungen verursachten Morbidität schon früher eingesetzt, allerdings mit dem Ziel deren Kontrolle besser zu lenken.

Ziel: Das Hauptziel dieser Dissertation war die Entwicklung, Validierung und Anwendung von Instrumenten zur Erfassung der durch verschiedene vernachlässigte Tropenkrankheiten auf verschiedenen geographischen Ebenen verursachten Morbidität und Krankheitslast. Dazu

wurden die folgenden drei Teilziele verfolgt: Erstens sollte im Rahmen der umfassenden Revision von allen globalen Krankheitslastschätzungen zum ersten Mal überhaupt die globale Krankheitslast von durch Nahrungsmittel übertragene Trematodeninfektionen erfasst werden. Zweitens sollten in epidemiologischen Feldstudien neue Anhaltspunkte in Bezug auf die individuelle Beeinträchtigung von Patienten mit Schistosomiasis (*S. haematobium* und *S. mansoni*) und/oder durch Bodenkontakt übertragene Würmern (*A. lumbricoides*, *T. trichiura*, Hakenwürmer) erarbeitet werden und die Resultate mit den aktuellsten Kennziffern zur durchschnittlichen Beeinträchtigung in der globalen Krankheitslaststudie verglichen werden. Drittens sollten einfache und billige anamnestischen Fragebogen, welche die von Schistosomiasis und von durch Bodenkontakt übertragenen Würmern verursachte Morbidität erfassen, insbesondere auf ihr Potenzial bei der Identifikation von Hochrisikogruppen und der Lenkung von Kontrollmassnahmen im Feld untersucht werden.

Methoden: Um das erste Teilziel anzugehen, wurde mittels eines breitgefächerten, systematischen Literaturreviews das derzeitige Wissen zu Manifestationen, Diagnostik, Behandlung und Epidemiologie von durch Nahrungsmittel übertragene Trematodeninfektionen zusammengetragen. Anschliessend wurde basierend auf den neusten Richtlinien die globale Krankheitslast von durch Nahrungsmittel übertragene Trematodeninfektionen erarbeitet.

Mit Bezug auf das zweite Teilziel wurde anfangs 2010 eine erste Querschnittsstudie mit 156 Schulkindern im Süden der Côte d'Ivoire durchgeführt. Kinder wurden parasitologisch auf *S. haematobium*, *S. mansoni*, *A. lumbricoides*, *T. trichiura*, Hakenwürmer und *Plasmodium* spp. getestet, klinisch untersucht, mit einem Teil eines Lebensqualitäts-Fragebogens befragt und eingeladen ein einem maximalen, mehrstufigen 20 m Pendellauftest teilzunehmen. Eine zweite Querschnittsstudie wurde Mitte 2010 im neu geschaffenen gesundheits-demographischen Beobachtungssystems (health demographic surveillance site; HDSS) in Taabo in Süd-Zentral-Côte d'Ivoire durchgeführt. 187 Erwachsene wurden parasitologisch auf die die selben Parasiten untersucht und mit einem kompletten Fragebogen zur Lebensqualität befragt. In der Analyse von beiden Studien wurden dann die verschiednen Testresultate einander gegenübergestellt.

Für das dritte Teilziel wurden 187 Erwachsene, die 2010 an der zweiten jährlichen parasitologischen Untersuchung des Taabo HDSS teilnahmen, und 146 Kinder und 439 Erwachsene, die 2011 an der dritten jährlichen parasitologischen Untersuchung des Taabo HDSS teilnahmen, mit anamnestischen Fragebogen befragt. Die Fragebogen enthielten Fragen zu Risikofaktoren, Anzeichen und Symptomen die oft mit Schistosomiasis und durch

Bodenkontakt übertragenen Würmern einhergehen. Die Fragebogenresultate wurden mit den parasitologischen Ergebnissen des Teilnehmers verglichen um die diagnostischen Fähigkeiten (Sensitivität, Spezifität, positiver und negativer Vorhersagewert) von einzelnen Antworten und Antwortkombinationen zu evaluieren.

Ergebnisse: Die Schätzungen zur globalen Krankheitslast von durch Nahrungsmittel übertragene Trematodeninfektionen implizieren, dass im Jahr 2005 56.2 Millionen Menschen weltweit infiziert waren, dass 7.9 Millionen an ernsthaften Komplikationen litten und dass 7'158 Menschen durch Cholangiokarzinome und cerebrale Infektionen starben. Diese Zahlen resultieren schliesslich in einer globalen Krankheitslast von 665'352 DALYs fürs Jahr 2005.

Mit Bezug auf die Messung der individuellen Beeinträchtigung konnte weder in den objektiv gemessenen Ergebnissen des maximalen, mehrstufigen 20 m Pendellauftest noch in den Resultaten der selbstausgefüllten Lebensqualitäts-Fragebogens ein Effekte von Schistosomiasis oder von durch Bodenkontakt übertragenen Würmern auf die physische Fitness der Schulkinder festgestellt werden. Dafür wurde eine statistisch signifikante Korrelation zwischen den Resultaten des Pendellauftest und des Fragebogens gefunden. In der zweiten Studie erzielten die mit *S. mansoni* oder *T. trichiura* infizierten Erwachsenen eine signifikant tiefere Lebensqualität (-16.4%; $p = 0.011$ und -12.6%; $p = 0.035$).

Die Resultate betreffend Sensitivität, Spezifität, positiven und negativen Vorhersagewerten der im anamnestischen Fragebogen der Pilotstudie von 2010 berücksichtigen Risikofaktoren, Anzeichen und Symptome enthüllten weder einen vielversprechenden Einzelindikator, noch eine vielversprechenden Indikatorenkombination. Die weitere Auswertung der Daten von der grösseren Studie von 2011 ist noch ausstehend.

Schlussfolgerung: Obschon einige noch offenen Probleme zum Konzept der globalen Krankheitslaststudien und Wissenslücken in Bezug auf durch Nahrungsmittel übertragene Trematoden aufgezeigt wurden und obschon bewusst zurückhaltende Schätzungen gemacht wurden, belegt die identifizierte Krankheitslast, dass durch Nahrungsmittel übertragene Trematodeninfektionen eine wichtige Gruppe von vernachlässigten Tropenkrankheiten darstellen. Insbesondere in den hochendemischen Regionen sind Anstrengungen zur Kontrolle von durch Nahrungsmittel übertragenen Trematoden unumgänglich.

Die Resultate zur individuellen Beeinträchtigung aufgrund von Schistosomiasis und durch Bodenkontakt übertragenen Würmern sind nicht eindeutig. Die signifikante Korrelation zwischen objektiv gemessener und selbstberichteter physischen Fitness von Schulkindern ist ein vielversprechender Hinweis für die allgemeinere Anwendbarkeit von Lebensqualität-Fragebogen. Und tatsächlich deuten die Zahlen zur reduzierten Lebensqualität von

Erwachsenen einen stärkeren negativen Effekt der Parasiteninfektionen als derzeit in den meisten Zusammenstellungen zur Krankheitslast angenommen wird. Die Notwendigkeit zur weiteren Innovation, Validation und Anwendung von systematischeren, holistischeren, wirklich interdisziplinären, feldbasierten, epidemiologischen Ansätzen um weitere Anhaltspunkte zu sammeln wird betont und mögliche nächste Schritte werden skizziert.

Das Projekt über die Möglichkeiten von weiter verfeinerten anamnestischen Fragebogen in der Lenkung der Kontrolle von Schistosomiasis und durch Bodenkontakt übertragenen Wurminfektionen ist noch in einem sehr frühen Innovationsstadium. Deshalb sind alle bisherigen Ergebnisse mit Vorsicht und als weitere Anregungen zu interpretieren. Wichtig zu Bedenken in diesem Zusammenhang: Wenn es möglich werden sollte die Effekte von vernachlässigten Tropenkrankheiten mit sorgfältig adaptierten und angewendeten Lebensqualitäts-Fragebogen zu eruieren, so scheint es auch vorstellbar, das krankheitsbezogene Risikofaktoren, Anzeichen und Symptome die Entwicklung von anamnestischen Fragebogen erlauben. Der mögliche Nutzen von solchen anamnestischen Fragebogen rechtfertigt weitere Anstrengungen. Optimalerweise sind diese Anstrengungen in breitere Forschungszusammenarbeiten eingebunden mit dem Ziel umfassendere Diagnsotik- und Behandlungs-Algorithmen zu erarbeiten. Detailierte Anregungen für weitere Studien sind in dieser Dissertation erwähnt.

Résumé

Contexte: Les maladies tropicales négligées (MTNs) comprennent un groupe d'infections, qui se produisent principalement dans les communautés pauvres et peuvent altérer le cours et l'issue d'une grossesse, la croissance durant l'enfance, le développement intellectuel, l'éducation et la productivité du travailleur. Une infection chronique à long terme peut entraîner une défiguration et la stigmatisation. D'où, les MTNs peuvent exacerber la pauvreté, et pourtant parce qu'il y a des opportunités commerciales limitées liées à celle-ci, la lutte contre elles reste largement négligée. Entre autres, les helminthiases telles que la schistosomiase (par exemple, causée par *Schistosoma haematobium* et *S. mansoni*), les géohelminthiases (par exemple, causée par *Ascaris lumbricoides*, *Trichuris trichiura* et les ankylostomes) et les trematodiases d'origine alimentaire (par exemple, causée par *Clonorchis sinensis*, *Opisthorchis viverrini*, *Fasciola* spp. et *Paragonimus* spp.) appartiennent au groupe des MTNs.

Dans les années 1990, pour mieux quantifier le fardeau attribué aux différentes maladies, infirmités et facteurs de risque, l'Organisation Mondiale de la Santé (OMS) et la Banque Mondiale ont élaboré un outil de mesure désigné sous le vocable «années de vie ajustées sur l'incapacité (AVAI). Les AVAI combinent les années de vie perdues pour cause de décès prématuré et les années vécues avec une invalidité en une seule mesure avec le but d'aider à mieux prioriser les activités de santé publique. En 2007, une révision complète de toutes les estimations du fardeau global attribué aux différentes maladies, infirmités et facteurs de risque a été lancée. Elle visait également à l'inclusion de pathologies non encore évaluées tels que les trematodiases d'origine alimentaire.

La popularité croissante des AVAI et des estimations du fardeau des maladies a suscité également un regain d'intérêt dans les paramètres épidémiologiques sous-jacents. Par exemple pour les MTNs, qui causent la morbidité plutôt que la mortalité, il est devenu évident que l'évaluation de la moyenne d'invalidité encourue par un patient est cruciale pour compiler correctement les données du fardeau global. Il est intéressant de noter l'usage dans un passé récent de questionnaires anamnestiques pour évaluer la morbidité causée par les helminthiases afin de mieux calibrer les efforts de lutte contre les helminthes.

Objectifs: L'objectif principal de cette thèse était de développer, valider et appliquer des outils d'évaluation de la morbidité et du fardeau causé par les MTNs à différentes échelles géographiques. Dans but de réaliser cet objectif principale, les trois objectifs spécifiques ci-après ont été poursuivis: (i) participer à l'estimation du fardeau global attribué aux différentes

maladies, infirmités et facteurs de risque et évaluer – pour la toute première fois – le fardeau global des trematodiases d'origine alimentaire, (ii) mener des enquêtes épidémiologiques en zone rural de Côte d'Ivoire pour générer de nouvelles évidences sur l'incapacité subie par les individus infectés par des schistosomes et/ou des géohelminthes et comparer ces résultats à des données récentes utilisées dans l'estimation du fardeau global, (iii) explorer le potentiel des questionnaires anamnestiques simples et à bas coût pour cerner la morbidité causé par la schistosomiase et les géohelminthiases dans le nouveau système de surveillance démographique (SSD) de Taabo, Côte d'Ivoire, afin d'identifier les groupes à haut risque et de diriger les efforts de lutte contre ces helminthiases.

Méthodes: Pour réaliser le premier objectif, une revue systématique a été menée afin d'établir l'évidence actuelle sur les conséquences, les techniques diagnostiques, les options de traitements et l'épidémiologie des trematodiases d'origine alimentaire. Le fardeau mondial des trematodiases d'origine alimentaire a ensuite été évalué en référence aux directives de la dernière révision du fardeau global.

Concernant le deuxième objectif, une première enquête transversale a été réalisée avec 156 écoliers dans le sud de la Côte d'Ivoire au début de 2010. Les enfants ont été examinés au moyen d'examens parasitologiques et cliniques, interrogés avec un questionnaire concernant la qualité de vie et invités à participer à une course navette de 20 mètres. En été 2010, une deuxième enquête transversale a été menée au sein du SSD de Taabo au sud-centre de la Côte d'Ivoire. Au total, 187 adultes ont subi des examens parasitologiques pour vérifier la présence et l'intensité des infections avec des helminthes et *Plasmodium* spp. En plus, les adultes ont été interrogés à l'aide d'un questionnaire concernant leur qualité de vie. Les résultats des différents enquêtes ont été comparés les uns aux autres.

Pour le troisième objectif, 187 adultes ont été interrogés par questionnaires anamnestiques dans le cadre de la deuxième enquête annuelle du SSD de Taabo en 2010 et 146 enfants et 439 adultes ont été interrogés par questionnaires anamnestiques pendant la troisième enquête annuelle du SSD de Taabo en 2011. Les questionnaires étaient structurés autour des facteurs de risque, les signes et les symptômes souvent associés à la schistosomiase et les géohelminthiases. Les résultats des questionnaires ont été comparés avec les résultats parasitologiques des participants afin d'évaluer le potentiel des questionnaires comme outil diagnostiques (sensibilités, spécificités, valeurs prédictives positives et négatives).

Résultats: L'évaluation du fardeau global attribué aux trematodiases d'origine alimentaire en 2005 indique que 56.2 millions de personnes ont été infectées, 7.9 millions ont souffert de séquelles graves et 7,1 millions sont morts à cause des cholangiocarcinomes et des infections

cérébrales. Ces chiffres se traduisent par un fardeau global de 665,352 AVAI pour l'année 2005.

Concernant l'invalidité subie par les individus infectés par des schistosomes et/ou des géohelminthes, les résultats de la première enquête transversale n'ont révélé aucun effet des infections sur la condition physique des écoliers – ni pour les résultats des courses navettes (mesure objective) ni pour les résultats des questionnaires (mesure subjective). Mais des corrélations statistiquement significatives ont été trouvés entre les résultats des courses navettes et les résultats des questionnaires. Dans la deuxième enquête transversale, les adultes infectés par *S. mansoni* ou *T. trichiura* rapportaient une réduction de la qualité de vie qui était statistiquement significatives (-16.4%, p = 0.011 et -12.6%, p = 0.035, respectivement).

Les résultats concernant, la spécificité, la sensibilité, les valeurs prédictives positives et négatives des facteurs de risque, des signes et des symptômes considérés dans le questionnaire anamnestique de l'enquête de 2010 n'ont révélé aucun indicateurs prometteurs pour le développement des questionnaires anamnestiques, qu'ils soient pris individuellement ou en combinaison. L'analyse des données recueillies pendant la plus grande enquête effectuée en 2011 est encore en cours.

Conclusion: Malgré les nombreuses questions non résolues sur le concept du fardeau global, les lacunes concernant les trematodiases d'origine alimentaire et notre décision de faire des estimations avec circonspection, l'évaluation du fardeau global révèle les trematodiases d'origine alimentaire comme groupe important parmi les MTNs. Surtout dans les zones de haute endémicité, les efforts pour contrôler les trematodiases d'origine alimentaire sont essentiels.

Les résultats sur l'invalidité subie par les individus infectés par des schistosomes et des géohelminthes sont ambigus. Mais la corrélation significative entre les mesures objectives et les mesures subjectives des aptitudes physiques des écoliers est un indicateur prometteur pour l'utilisation de questionnaires sur la qualité de la vie en général. En fait, les chiffres concernant la réduction de la qualité de vie des adultes indiquent un effet négatif de ces infections parasitaires qui est plus élevée que précédemment estimée dans la compilation du fardeau des maladies. La thèse de doctorat souligne la nécessité de poursuivre l'innovation, la validation et l'application des approches systématiques et interdisciplinaires, qui se basent sur des études de terrain pour recueillir nouvelle évidence sur l'invalidité causée par les helminthiases. Une perspective d'avenir est décrite dans la présente thèse.

Le projet sur le potentiel et l'amélioration des questionnaires anamnestiques pour guider les efforts de lutte contre la schistosomiase et les géohelminthiases est encore dans une phase

d'exploration. En conséquence, les résultats présentés dans cette thèse sont plutôt suggestifs et doivent être interprétés avec prudence. Mais s'il est éventuellement possible d'évaluer les effets des MTNs avec des questionnaires de qualité de vie, il est aussi concevable que les facteurs de risque, les signes et les symptômes associés aux helminthiases permettent l'élaboration d'un questionnaire anamnestique. Les avantages potentiels d'un questionnaire anamnestique justifient des efforts additionnels. Idéalement, ces efforts devront se déroulent dans le cadre d'une collaboration de recherche plus compréhensive, visant à l'élaboration des algorithmes intégratifs pour la diagnose et le traitement des différents syndromes. Des suggestions détaillées pour des futures études ont été fournies dans la présente thèse.

1. Introduction

This chapter provides a succinct overview of the life cycle, geographical distribution and burden (section 1.1), epidemiology (section 1.2), pathological consequences and clinical manifestations (section 1.3), diagnosis (section 1.4), treatment (section 1.5) and control (section 1.6) of schistosomiasis and soil-transmitted helminthiasis. These two diseases belong to the neglected tropical diseases (NTDs).[1] Another important cluster of NTDs considered in this thesis are food-borne trematodiases. The characteristics of the food-borne trematodiases are comprehensively discussed in the first research article (chapter 5), and hence not covered here. The final two sections of this introduction highlight the importance of assessing human health on a global (section 1.7) and on a local scale (section 1.8).

1.1. Geographical distribution, burden and life cycle of schistosomiasis and soil-transmitted helminthiasis

1.1.1. Schistosomiasis

Schistosomiasis, also known as bilharzia, or blood fluke infection, or snail fever is a parasitic disease caused by trematode worms of the genus *Schistosoma*.[2-5] The six species *Schistosoma guineensis*, *S. haematobium*, *S. intercalatum*, *S. japonicum*, *S. mansoni*, and *S. mekongi* are known to infect humans and considered endemic in 76 countries (Figure 1).[2-6] Most human infections with *S. haematobium* and *S. mansoni* occur in sub-Saharan Africa, but both species are also present on the Arabian Peninsula and *S. mansoni* remains endemic in parts of Latin America and the Caribbean.[2-5] *S. guineensis* and *S. intercalatum* are only of regional importance in Central Africa.[4-6] *S. japonicum* is found in East and Southeast Asia and *S. mekongi* exist only along the Mekong River.[2-5]

Currently, 779 million people are believed to be at risk of schistosomiasis worldwide and 207 million infected with schistosomes.[7] 120 million people may suffer from clinical manifestations and 15,000-280,000 may die due to schistosomiasis each year.[8,9] The global burden of schistosomiasis has been estimated at 1.7-4.5 million disability-adjusted life years (DALYs),[8,9] but based on revised disability assessments, estimates of up to 70 million DALYs have been put forth.[2,10,11]

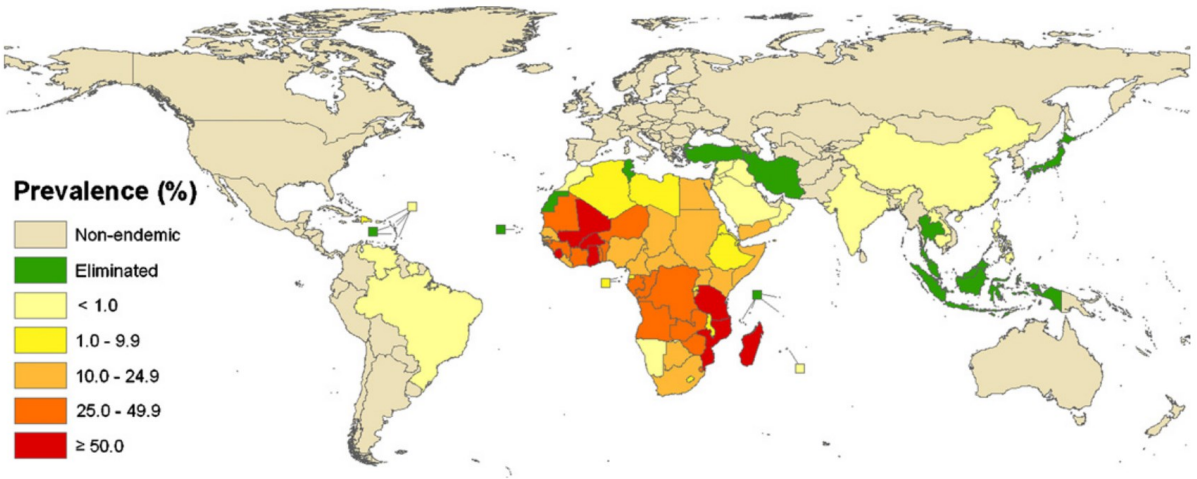

Figure 1. Global distribution of schistosomiasis. The map highlights countries with different schistosomiasis prevalences. (Source: reference [12]).

The schistosomes' life cycles include different species of aquatic and amphibious snails as intermediate hosts (Figure 2). Aquatic snails from the genus *Bulinus* are the intermediate hosts for *S. guineensis*, *S. haematobium* and *S. intercalatum*, whereas aquatic *Biomphalaria* and *Tricula aperta* snails act as intermediate hosts for *S. mansoni* and *S. mekongi*, respectively. Amphibious snails from the genus *Oncomelania* serve as intermediate hosts for *S. japonicum*.[3-5]

Human infections begin with the exposure of the skin to freshwater bodies, which contain infected intermediate host snails. The infected snails release cercariae that penetrate the intact exposed skin.[2-5] In the human host, cercariae develop into schistosomula and migrate with the blood stream via the lungs and the heart to the liver. In the liver, the parasites mature and pair off. Finally, the adult worm pairs further migrate to the mesenteric vessels of the bowel or bladder, where they remain.[2-5] Four to six weeks after the initial human host infection, adult females start producing hundreds (*S. haematobium*, *S. mansoni*) to thousands (*S. japonicum*) of eggs each day for several years.[3,5] One part of the eggs may become trapped in the tissue of organs, causing inflammation and severe morbidity in the chronic stages of the disease. Another part of the eggs are excreted in the host's urine (*S. haematobium*) or feaces (other species), have to reach freshwater bodies, and hatch into miracidia, which are infective to intermediate host snails for about 8-12 hours. After about one month, infected snails release cercariae.[2-5]

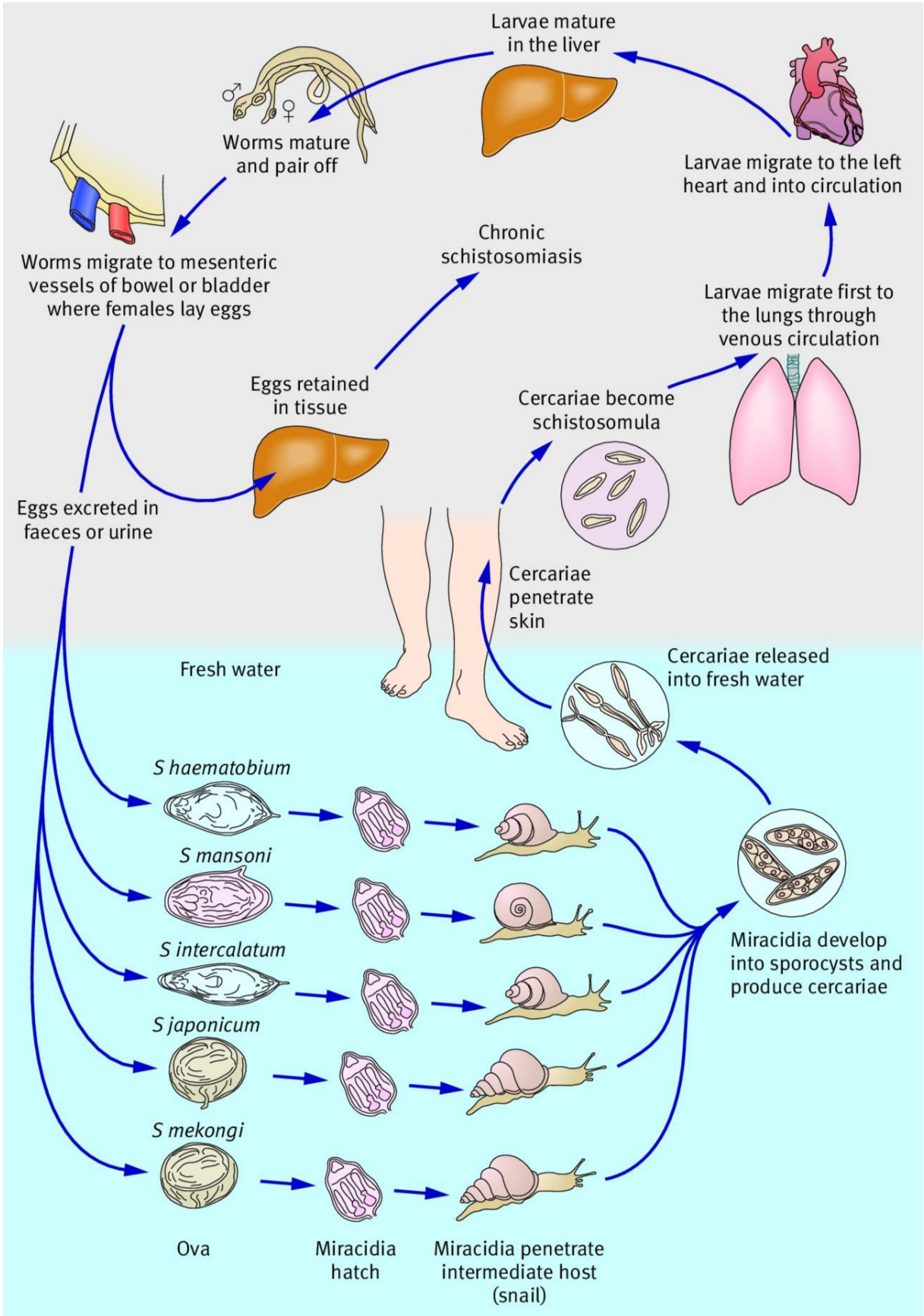

Figure 2. Life cycle of schistosomiasis. (Source: reference [2]).

1.1.2. Soil-transmitted helminthiasis

Soil-transmitted helminthiasis is a parasitic disease caused by intestinal nematode worms, which undergo parts of their development in the soil.[13,14] The most common soil-transmitted helminths are the whipworms (*Trichuris trichiura*), the roundworms (*Ascaris lumbricoides*), and the hookworms (*Ancylostoma duodenale* and *Necator americanus*).[13,14] Soil-transmitted helminth infections are one of the most common human infection, occur worldwide, but are most prevalent in tropical and sub-tropical regions (Figure 3).[13-15] High prevalences of all soil-transmitted helminth infections have been reported from South, East, and Southeast Asia, from sub-Saharan Africa and parts of Latin America and the Caribbean.[13-15] Of note, socio-economic development and sustained control efforts helped to reduce *T. trichiura* prevalence levels in East Asia and Latin America.[13]

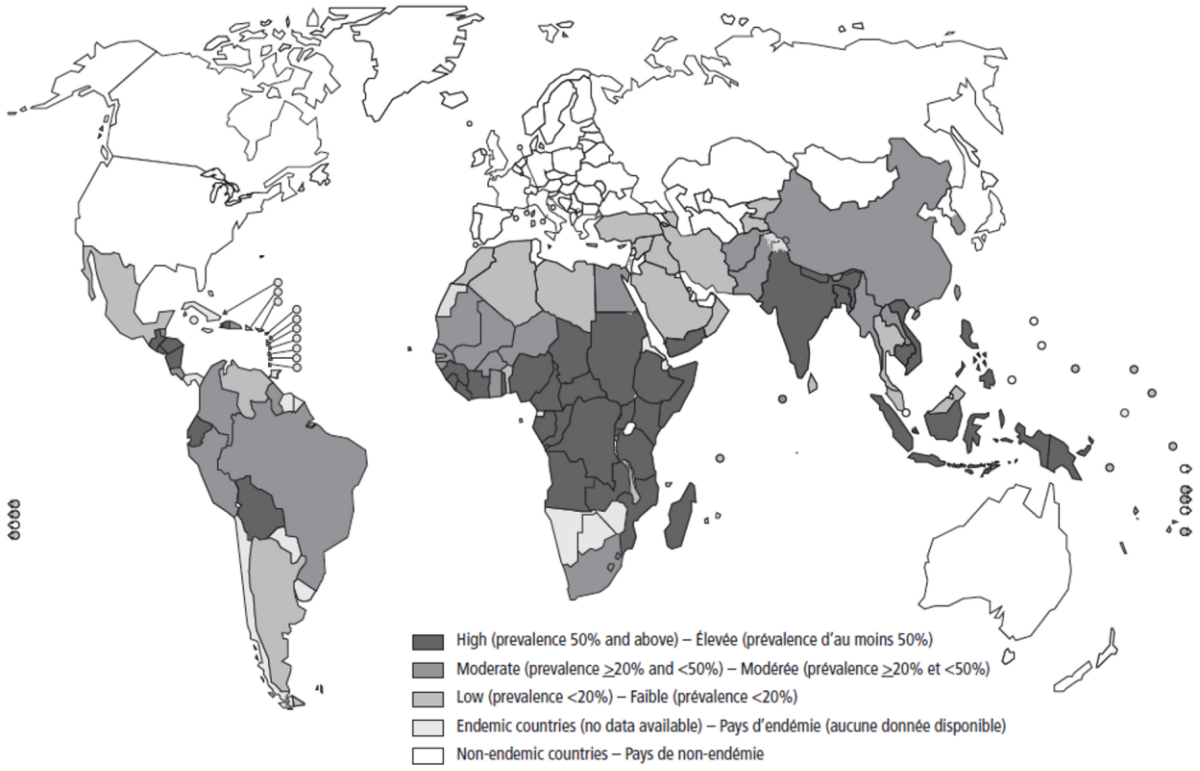

Figure 3. Global distribution of soil-transmitted helminthiasis. The map highlights countries with different soil-transmitted helminthiasis prevalences. (Source: reference [16]).

Globally, 4,211 million people are currently considered at risk of ascariasis, 3,212 million people at risk of trichuriasis, and 3,195 million people at risk of hookworm infections.[8,9,15] 807-1,221 million, 604-795 million, and 576-740 million people are estimated to be infected with *A. lumbricoides*, *T. trichiura*, and hookworm, respectively.[8,9,14,15] Hence, more than a

billion people harbor at least one soil-transmitted helminth species, but concurrent infections with multiple species are common.[17-20] 350 million, 220 million, and 150 million people of those infected with *A. lumbricoides*, *T. trichiura*, and hookworm, respectively, may suffer from clinical manifestations.[8,9] Annual numbers of deaths due to *A. lumbricoides*, *T. trichiura*, and hookworm infections range between 3,000-60,000, 3,000-10,000, and 3,000-65,000, respectively.[8,9] These figures result in global burden estimates of 1.8-10.5 million, 1.0-6.4 million, and 0.1-22.1 million DALYs due to *A. lumbricoides*, *T. trichiura*, and hookworm infections, respectively.[8,9,14]

Humans are the only major definitive host of soil-transmitted helminths.[14] The life cycles of soil-transmitted helminths can be divided into three types: direct, modified direct and skin penetration.[13] *T. trichiura* has a direct life-cycle, indicating that already embryonated eggs are excreted by infected individuals. Excreted eggs do not necessarily have to reach the soil as they do not require a development stage there. After the eggs are carried back to the mouth via contaminated fingers or raw food (e.g., fruits and vegetables) and eventually swallowed, they hatch in the intestine and infect individuals within 2-3 hours. The released larvae pass to the caecum and colorectum, mature into adults within about 12 weeks and the females start producing 3,000-5,000 new eggs per day.[13,14]

A. lumbricoides have a modified direct life-cycle, which means that, before being swallowed again, the excreted eggs have to be 1-4 months in damp warm soil to develop an embryo (Figure 4).[13] In the human host, hatched *A. lumbricoides* larvae penetrate the intestinal mucosa, enter the bloodstream and then the lungs, migrate up the trachea to the larynx, are swallowed a second time and reach again the intestine, where they remain. During this migration, the parasites undergo further development stages and finally become adult worms 9-11 weeks after the hosts' initial egg ingestion.[13,14] The egg output of a female *A. lumbricoides* worm may be as high as 200,000 eggs per day.

Similar to *A. lumbricoides*, hookworm undergoes certain development stages outside the human body. In damp shaded soil, excreted eggs hatch into larvae and molt twice before becoming infective third-stage larvae (L_3).[13,14] These larvae cannot survive in water, move towards oxygen, and are therefore most numerous in the top layer of the soil, where they can survive for 1-2 years.[13] Unlike the other soil-transmitted helminths, the larvae directly penetrate the human skin if in contact and only *A. duodenale* is also orally infective. Again similar to *A. lumbricoides,* hookworm larvae then enter the bloodstream and reach via the lungs, trachea, larynx and oesophagus the small intestine, where they mature and each female produces 9,000-10,000 (*N. americanus*) or even 25,000-30,000 (*A. duodenale*) eggs per day

for several years.[13,14] About 5-9 weeks are needed from initial host skin penetration until the production of the first eggs.[14]

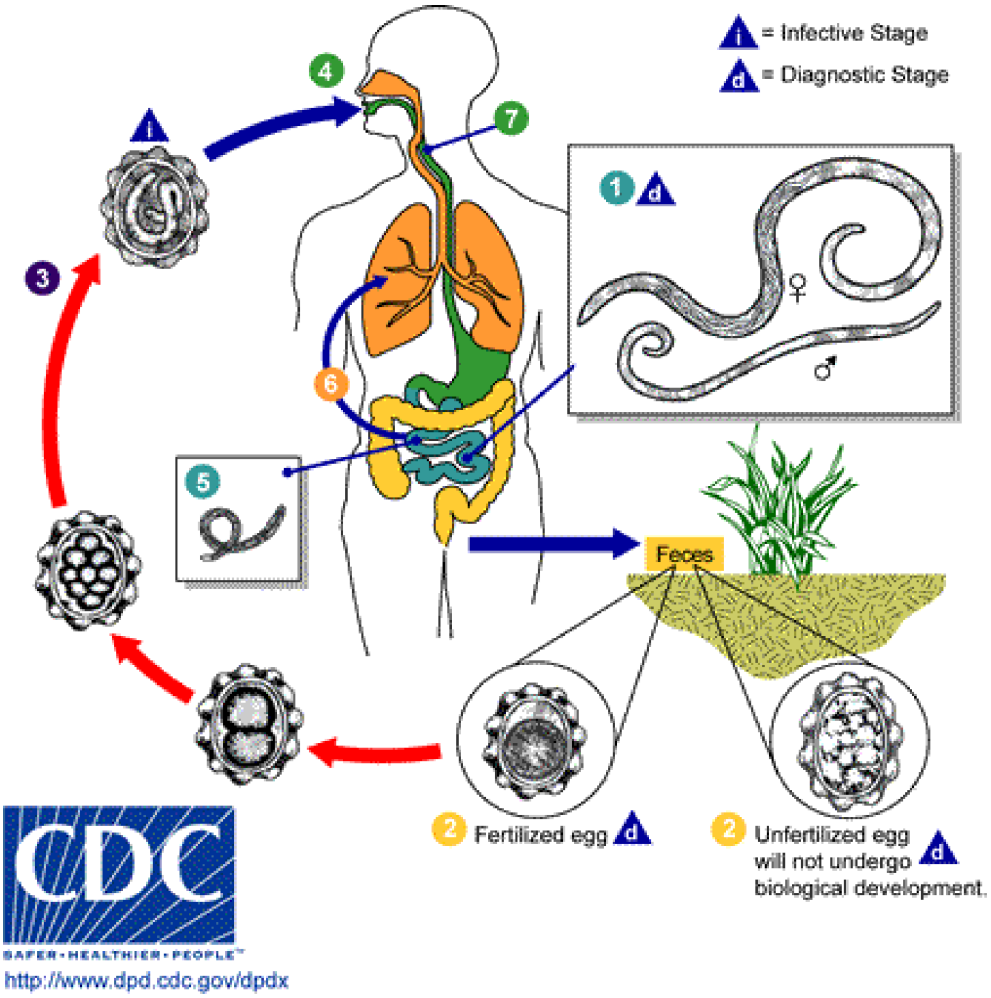

Figure 4. Life cycle of ascariasis. (Source: http://dpd.cdc.gov/dpdx/HTML/Ascariasis.htm).

1.2. Determinants and patterns of schistosomiasis and soil-transmitted helminthiasis transmission

1.2.1. Schistosomiasis

Due to the importance of the intermediate host snails, schistosomiasis transmission is highly dependent on interrelated environmental factors.[2] The climate (temperature, precipitation), hydrology and relief (freshwater quality, flow velocity), and vegetation are key determinants as most snails prefer moderately flowing, shallow, more or less shady freshwater bodies or marshlands, with plenty of submerged, emergent or intrusive vegetation that offer sufficient food and egg deposition places.[5,7,21-23] However, all intermediate host snails are able to aestivate and thereby enable the schistosomes to survive temporary dry seasons.[5] Man-made environmental changes such as water resources development projects for flood control, drinking water provision, hydropower generation, irrigation,[3,5,7,24-28] or mining projects[5,29,30] may further the spread of schistosomiasis without appropriate mitigation activities. Furthermore, development projects may lead to more or less voluntary migration and the introduction of the parasites in previously non-endemic areas.[3,5,29,30]

Beyond environmental parameters, land use patterns, and migration, there is a variety of socio-economic and behavioral factors, which influence disease transmission. Schistosomes thrive where inadequate sanitation and poor hygiene allow them to establish their life cycles.[5,31-33] Of note, animal reservoir hosts play an important role in *S. japonicum* transmission, whereas their role in *S. mansoni* transmission might be of subordinate importance and negligible in *S. haematobium* transmission.[4,5] Infection intensity in humans depends on the frequency, duration and surface of body in contact with contaminated water and it is therefore intimately connected with human behavior such as farming, fishing, water fetching, washing or swimming.[5,34,35] Infection may increase exponentially with water contact duration, peaking at ~30 minutes,[2] and surface of body exposed to infested water.[5]

The complex social-ecological interactions act on the snail intermediate hosts, the human definitive host, and the parasites and result in focalized geographical distribution patterns of schistosomiasis.[4,5,33] For instance, Yapi and colleagues found in 2005 that rice cultivation may increase the risk of schistosomiasis in the savannah zone of Côte d'Ivoire, but not in the forest zone.[36] Exemplary for NTDs, schistosomiasis primarily affects socio-economically deprived populations with insufficient information, education and access to health care.[5,31,33,34] Clustering occurs even within the same village and between individuals.[4,5,33] A minority of

people harbors the majority of parasites and sheds most of the eggs in a community.[37-39] Highest prevalence rates and infection intensities are commonly found in school-aged children, adolescents and young adults.[4,5,33] The decrease in older ages have been explained with changing behavior, partially acquired immunity and increasingly incurred tissue fibrosis, which may prevent eggs from reaching the exterior.[4,5] Sex-related patterns may also occur, depending on cultural, behavioral, professional and religious factors.[4]

1.2.2. Soil-transmitted helminthiasis

A. lumbricoides and hookworm undergo important stages of their life cycle in the soil and the survival of all free living stages of soil-transmitted helminths (i.e., including *T. trichiura*) depends on the availability of suitable soil habitats.[13,14] Land surface temperature and atmospheric humidity are crucial parameters as the free living stages cannot withstand temperatures below 5-10°C and above 38-40°C or desiccation.[40] However, unlike *A. lumbricoides* and *T. trichiura* ova, the free living larvae of hookworm have some limited motility and can move downward into the soil to escape from potentially fatal temperatures or desiccation.[13,40] The normalized difference vegetation index (NDVI) and elevation models have been used for prediction of soil-transmitted helminth prevalences[40] as the vegetation and relief are ecologically linked with temperature and humidity.

At smaller spatial scale, socio-economic factors and human behavior become increasingly important.[40] As with the schistosomes, soil-transmitted helminths thrive wherever suitable environmental conditions are coupled with impoverished areas characterized by inadequate sanitation and hygiene, poor education and overcrowding.[13-15,31,32,40,41] Behavioral factors such as the use of faeces as fertilizers, hand washing patterns, food preparation habits and geophagia – the eating of soil – potentiate the risk of infection.[13,42]

Clustering between communities and households and highly aggregated distributions among individuals have also been observed with soil-transmitted helminths. Individuals' pre-disposition may be influenced by genetic, nutritional, socio-economic and behavioral factors.[13,14,19,43-51] Prevalence rates and intensities of *T. trichiura* and *A. lumbricoides* are highest among school-aged children and adolescents,[13,14,40] whereas hookworm infections and infection intensities seem to increase more steadily with age or plateaus in adulthood.[14,52,53] No consistent sex-specific patterns have been reported, but may also occur depending on cultural, behavioral, professional and religious determinants.

1.3. Pathological consequences and clinical manifestations of schistosomiasis and soil-transmitted helminthiasis

1.3.1. Schistosomiasis

Schistosomiasis progresses usually in an acute, a chronic and an advanced phase. However, the often described, gradual and clearly differentiated pathological consequences and clinical manifestations according to the parasites development stage may appear in people who are infected for the first time (e.g., travelers, immigrants), but are usually blurred in people living in endemic areas by the endless series of epidemiological, immunological, and physiological interactions (e.g., re-infection, super-infection, and co-infection). Furthermore, the aggregated distribution of parasites among human hosts and the diverse distribution within infected individuals result in a variety of pathological consequences and clinical manifestations and many schistosomiasis cases remain rather asymptomatic.[2,5]

As an early manifestation, a limited dermatitis may arise at the site where the schistosome cercariae penetrated the skin and particularly people infected for the first time may develop an itchy rash, which is less severe and should not be confused with "swimmer's itch".[2-5] After cercarial invasion, during the schistosomula migration, maturation, pairing and beginning of egg deposition into host tissue, an acute hypersensitivity reaction may lead to acute schistosomiasis, also known as Katayama syndrome.[2-5,54] Symptoms in this phase may include fever, fatigue, headache, loss of appetite, nausea, myalgia, non-productive cough, right upper quadrant pain and diarrhoea (with or without presence of blood).[2-4,54]

Adult worms by themselves cause little or no pathology and the lesions that occur during infection are mainly caused by the increasing number of eggs that were laid in the organ walls and become trapped in the host's tissue.[2,4,5] Via collateral vascular bypasses, *Schistosoma* eggs can also reach other organs in the host's body.[5] The eggs evoke granuloma formation, which destroys the eggs, but results in fibrosis in the host tissue.[2-5] After years of chronic infection, sustained local inflammation and fibrosis leads to the advanced stage of the disease with severe complications at the sites of maximal egg accumulation.[2-5] Complications include intestinal complaints, ascites, hepatosplenic inflammation and hepatosplenomegaly, and liver fibrosis.[2-5] Progressive obstruction of the blood flow results in portal hypertension, varices and intestinal bleeding.[2-4] Particularly in case of *S. haematobium*, obstructive and inflammatory disease in the urinary tract, bladder calcification and renal failure occurs.[2-5] Unlike early lesions, late obstructive fibrous lesions respond poorly to antischistosomal treatment.[5]

Additional symptoms in the chronic and advanced phase include colicky abdominal pain, diarrhoea that may alternate with constipation, and blood in stool as gastrointestinal complaints.[2-5] Urinary disease caused by *S. haematobium* presents with haematuria, dysuria, lower abdominal pain and renal colic.[2-5] Population studies indicate that schistosomiasis causes anaemia, malnutrition, growth retardations, reduced exercise tolerance, cognitive and memory impairment and adversely affects maternal health and the unborn fetus.[2,4,5,10,11] Such subtle or indirect morbidity remains difficult to measure, but received more attention over the last years as severe morbidity becomes less common due to treatment efforts with modern antischistosomal drugs.[4,10,11] Schistosomiasis may also influence the individual's susceptibility to HIV, malaria, tuberculosis, viral hepatitis and other helminth infections and alter the natural history of these diseases.[2,10,11] In about a third of infected women genital disease may occur and advanced genitourinary schistosomiasis has been associated with dyspareunia and infertility.[2-5,10,11] One of the most severe clinical outcome of schistosome infection is neuroschistosomiasis, resulting from aberrant migration of adult worms and/or egg accumulation in the spinal cord and the brain.[2-5,55,56] An association between *S. haematobium* infection and bladder cancer has been suggested.[2-5,57]

1.3.2. Soil-transmitted helminthiasis

Pathological consequences and clinical manifestations of soil-transmitted helminthiasis is – similar to other helminth infections – often not overt, blurred by frequent re-infection, super-infection and co-infection, and strongly related to the number of worms in the human host, i.e., infection intensity.[13,14] After ingestion, hatching, and maturation, adult *T. trichiura* attach themselves to the mucosa of the large intestine, thereby causing mucosal damage.[13,14,58] This leads to haemorrhages, mucopurulent and bloody stools, colitis, and acute phase immune response may induce *Trichuris* dysentery syndrome, whose symptoms include anaemia, clubbing of fingers and rectal prolapse.[13,14,58] Mucosal damage can also facilitate the invasion of other infections.[13] Additional symptoms of trichuriasis are distension, flatulence, epigastric pain, vomiting, anorexia and weight loss.[13,14,58] In children, severe anaemia, negative impact on nutritional status, and retardation of physical and intellectual growth can occur.[13,14]

Pathology due to *A. lumbricoides* is the result not only of the adults residing in the small intestine, but also by adults in abnormal locations and the larvae migrating through the lungs.[13,14,59] Larval migration causes pathology and symptoms from their physical presence and elicited inflammatory reactions.[13] During larval lung passage, eosinophilic pneumonia

(Löffler's syndrome) may occur with skin rash, fever, wheezing, cough, dyspnoea and asthma.[13,14,59] In addition. large numbers of adults in the small intestine may lead to nausea, anorexia, vomiting, diarrhoea, abdominal distension, intestinal colic, volvulus and obstruction.[13,14,59] Wandering *A. lumbricoides* can cause abnormal situations, i.e., blocking or perforation of the bowel, appendicitis, invasion of the genital tract, blocking of the ampulla of Vater or the common bile duct, and invasion of the liver.[13,14] Hepatobiliary ascariasis is not uncommon in endemic settings, elicit cholangitis, cholecystitis, hepatolithiasis, and liver abscess with associated fever, right upper abdominal pain and jaundice.[13,14] Ascariasis-related damage in the intestine can result in malabsorption, malnutrition, vitamin A deficiency and night blindness, as well as growth and cognitive impairment.[13,14]

Hookworm infections may cause pathological consequences and clinical manifestations at three stages.[13] People who are infected for the first time (e.g., travelers, immigrants) may experience an itchy vesiculation and postulation (ground itch) at the site of skin invasion (usually feet and hands).[13,14,53] Also mainly in people being infected for the first time, larval migration through the lungs can cause non-specific asthma and bronchitis with a dry cough, wheezing, dyspnoea and fever.[13,14,53] In established infections, mainly in inhabitants of endemic areas, the attachment of the hookworms to the intestinal mucosa and blood sucking results in chronic blood loss and leads to iron deficiency and hookworm anaemia.[13,14,53] Protein loss due to enteropathy may lead to oedema or even anasarca.[13,14,53] Other symptoms of hookworm disease include fatigue, anorexia, vomiting, nausea, headache, digestive disturbances and dyspepsia, epigastric discomfort and pain, diarrhoea and blood in stool, anaemic pallor and koilonychia, breathlessness, heart palpitation and heart failure, reduced work capacity, growth stunting and impaired cognition in children.[13,53] Women of child-bearing age, pregnant women, and children are usually the most susceptible to hookworm disease and anaemia due to their underlying iron and nutritional status, with adverse effects on pregnancy and birth outcome, school achievements and wage earning potential in adulthood.[13,14,53]

1.4. Diagnosis of schistosomiasis and soil-transmitted helminthiasis

1.4.1. Schistosomiasis

Microscopic parasite egg detection in urine (in case of *S. haematobium*) and stool (in case of *S. mansoni*, *S. japonicum*, *S. intercalatum*, *S. guineensis* and *S. mekongi*) remains the gold

standard for the diagnosis of schistosomiasis.[2-5,12,60] Filtration, sedimentation, and/or centrifugation of collected urine samples is applied to diagnose urinary schistosomiasis.[2,4,5,12,60] The rapid, simple, and inexpensive Kato-Katz thick smear stool examination is probably the most widely used technique to diagnose intestinal schistosomiasis and requires a minimum of 40-50 mg of feaces.[2-5,12,60,61] Direct faecal smear is also commonly used and formalin-based concentration, sedimentation, and flotation techniques have been put forth to increase diagnostic accuracy.[2-4,12,62-64] Such direct parasitological methods, if correctly performed, offer a specificity of 100%. However, due to the parasites pre-patent period, individual day-to-day variation and variation within the excreta, sensitivity varies with intensity of infection, the number of consecutive urine or stool samples collected and the number of microscope slides prepared and examined and may reach 70-100%.[2,4,5,65-71] Infection intensities are usually measured as the number of eggs detected in 10 ml of urine (urinary schistosomiasis) or the number of eggs detected in a small amount of stool (e.g., 42 mg using the Kato-Katz thick smear), which is then translated to the number of eggs per gram of stool (EPG; intestinal schistosomiasis). Thus defined infection intensities are often considered as indicator for the worm-burden in the host and categorized according to WHO guidelines (Table 1).[33]

Table 1. Classification of infection intensities for *S. haematobium* and *S. mansoni*.

Parasite	Infection intensity		
	Light	**Moderate**	**Heavy**
Schistosoma haematobium	<50 eggs/10 ml urine	---	≥50 eggs/10 ml urine, or visible haematuria
Schistosoma mansoni	1-99 EPG	100-399 EPG	≥400 EPG

This table is based on reference [33]. EPG = eggs per gram of stool.

Indirect diagnostic methods aim at the detection of pathological consequences, clinical manifestations, human antibodies or parasitic antigens. Indirect methods include anamnestic questioning and reagent strips testing for blood in urine (urinary schistosomiasis) or stool (intestinal schistosomiasis) or radiological imaging techniques and ultrasonography, and immunodiagnostic tests such as enzyme-linked immunosorbent assays (ELISA) and indirect haemagglutination assays (IHA).[2,4,5,12,72,73] These methods are comparatively unspecific, but considered particularly useful in patients who are not excreting eggs and in field studies for community screening.[2-4,72,73] Recently, first promising results have been reported for urine circulating cathiodic antigen tests.[2,3,5,12,74-76] A highly specific, sensitive, but also expensive

molecular diagnostic approach is based on polymerase chain reaction (PCR), which identifies schistosome DNA in faeces, sera and plasma.[2,12,73]

1.4.2. Soil-transmitted helminthiasis

Analogously to the diagnosis of schistosomiasis, soil-transmitted helminths can be diagnosed directly by identification of parasites and their eggs or indirectly by detection of pathological consequences, clinical manifestations, human antibodies and parasitic antigens. Kato-Katz thick smear stool examination is widely used for soil-transmitted helminthiasis and recommended as a standard method by WHO.[13,14,60,61] Direct faecal smear, concentration and flotation methods are potential alternatives and particularly the latter may even have a higher test accuracy than the Kato-Katz technique.[13,14,63,64,77-80] Infection intensities are also measured as the number of eggs detected in a small quantity of stool, which are then translated to numbers of EPG. EPG are considered as an indicator for the host's worm burden, and categorized according to WHO guidelines (Table 2).[33]

Table 2. Classification of infection intensities for soil-transmitted helminths.

Parasite	Infection intensity		
	Light	**Moderate**	**Heavy**
Trichuris trichiura	1-999 EPG	1,000-9,999 EPG	≥10,000 EPG
Ascaris lumbricoides	1-4,999 EPG	5,000-49,999 EPG	≥50,000 EPG
Hookworms	1-1,999 EPG	2,000-3,999 EPG	≥4,000 EPG

This table is based on reference [33]. EPG = eggs per gram of stool.

Indirect serological diagnosis with ELISA is an alternative diagnostic method, but has a limited specificity due to cross-reactivity.[13,81] Again, PCR to detect helminth DNA in stool specimens offers high specificity and sensitivity.[13,81] Radiological imaging and ultrasonography may be considered as complementary tools.[13,14]

1.5. Treatment of schistosomiasis and soil-transmitted helminthiasis

1.5.1. Schistosomiasis

Drugs against the two most prevalent schistosome species, *S. haematobium* and *S. mansoni*, which are also in the main focus of the present thesis, are listed in Table 3, along with recently reported cure rates, egg reduction rates, and deduced efficacy. Frequently recommended oral dosages are presented in Table 4. All listed drugs are currently on the World Health Organization (WHO) model list of essential drugs[82] and generally considered safe with restrained use mainly among pregnant or breast feeding women and infants.

Of note, oxamniquine is currently available in only very few countries, but the manufacturer has assured WHO to continue the production of this antischistosomal compound for the foreseeable future.[5] However, oxamniquine is only active against *S. mansoni*.[4,5,12] The artemisinin derivatives artemether and artesunate can be used as chemotherapy or chemoprophylaxis against schistosomiasis, but they are currently among the most potent antimalarials and biological and epidemiological issues such as the fear of resistance in *Plasmodium.* spp. have to be clarified before routine use of these substances may be recommended.[2-5] Hence, the current mainstay of antischistosomal treatment is praziquantel, which is active against all schistosome species parasitizing humans.[2-5,12] Adjuvant treatment may be indicated in cases with severe complications.[2-5,54,56] Importantly, the prices of most anthelminthic drugs have plummeted as the patents run out. For instance, a 600 mg tablet of praziquantel now costs approximately US$. 0.08, and hence treatment of a school-aged child costs less than US$ 0.30-0.40.[33,83] Furthermore, donations of anthelminthic drugs have been made by the pharmaceutical industry over the last years.[84]

Table 3. Oral chemotherapeutic treatment against schistosomiasis, reported cure and egg reduction rates, and deduced efficacy.

Parasite	Drug	Cure rate	Egg reduction rate	Efficacy[a]	Source
S. haematobium	Praziquantel[b]	44-93%	84-97%	+++(++)	85,86
	Artesunate[c]	20-100%	55-100%	++(+++)	85,86
	Artemether[c]	25%	ND	++	85,86
S. mansoni	Oxamniquine[d]	60-100%	up to 100%	++++(+)	5,85
	Praziquantel[b]	73-90%	89-94%	++++(+)	85,86
	Artemether[c]	50-100%	up to 100%	+++(++)	85,86
	Artesunate[c]	23-100%	59-100%	++(+++)	85,86

All drugs are currently on the WHO model list of essential drugs, but artesunate and artemether as antimalarials and not as antischistosomals.[82] ND = not determined. [a]Treatment efficacy: +++++ = cure rate and egg reduction rate of 80-100%; ++++ = cure rate and egg reduction rate of 60-79%; +++ = cure rate and egg reduction rate of 40-59%; ++ = cure rate and egg reduction rate of 20-39%; + = cure rate and egg reduction rate of 0-19%. [b]Limited resistance documented. [c]Used as chemotherapy or chemoprophylaxis; currently among the most potent antimalarials. [d]Limited resistance documented; no activity against *S. haematobium*.

Table 4. Frequently recommended oral dosage of antischistosomal chemotherapeutic treatment.

Drug	Recommended oral dose	Source
Praziquantel[a]	40 (or 60) mg/kg single or divided doses	2-5,85
Oxamniquine	15-60 mg/kg single or divided doses	5,85
Artemether	Chemoprophylaxis: 6 mg/kg once every 2-4 weeks	2,3,85,86
	Chemotherapy: varying dosages	85,86
Artesunate	Chemoprophylaxis: 6 mg/kg once every 2-4 weeks	2,85,86
	Chemotherapy: varying dosages	85,86

[a]Praziquantel is currently the treatment of choice.

1.5.2. Soil-transmitted helminthiasis

Drugs against *T. trichiura*, *A. lumbricoides*, and hookworm and respective cure rates, egg reduction rates, and deduced efficacy are listed in Table 5. Anthelminthics on the WHO model list of essential drugs[82] are indicated in bold. Recommended oral drug dosage is shown in Table 6. Again, the listed drugs are considered safe, with restraints mainly for pregnant or breast feeding women and infants.

Table 5. Oral chemotherapeutic treatment against soil-transmitted helminthiasis, reported cure and egg reduction rates, and deduced efficacy.

Parasite	Drug	Cure rate	Egg reduction rate	Efficacy[a]	Source
T. trichiura	**Mebendazole**	19-78%	52-93%	+(++++)	85,87,88
	Albendazole	0-99%	0-92%	+(++++)	85,87-91
	Tribendimidine	33%	76%	++(++)	85
	Pyrantel pamoate[b]	11-38%	52%	+(++)	85,87,90,91
	Ivermectin	11-35%	43-59%	+(++)	85,89,90
	Levamisole	9-10%	42%	+(++)	85,87
	Diethylcarbamazine	3%	20%	+(+)	90
A. lumbricoides	**Levamisole**	87-100%	92-100%	+++++	85,87
	Pyrantel pamoate[b]	85-100%	88-100%	+++++	85,87,90,91
	Tribendimidine	98%	96%	+++++	85
	Mebendazole	78-100%	96-100%	++++(+)	85,87,88
	Ivermectin	78-100%	up to 100%	++++(+)	85,89,90
	Albendazole	70-100%	87-100%	++++(+)	85,87-91
	Piperazine	62-85%	ND	++++(+)	85
	Diethylcarbamazine	17-31%	18-77%	+(+++)	85,90
Hookworm[c]	Tribendimidine	78-86%	99%	++++(+)	85
	Albendazole	40-100%	64-100%	+++(++)	85,87-91
	Mebendazole	8-91%	0-98%	+(++++)	85,87,88
	Pyrantel pamoate[b]	9-88%	56-75%	+(++++)	85,87,90,91
	Levamisole	0-93%	61%	+(++++)	85,87
	Ivermectin	0-64%	0-92%	+(++++)	85,89,90
	Diethylcarbamazine	22-26%	19-36%	++	85,90

Drugs currently on the WHO model list of essential drugs[82] are indicated in bold. ND = not determined. [a]Treatment efficacy: +++++ = cure rate and egg reduction rate of 80-100%; ++++ = cure rate and egg reduction rate of 60-79%; +++ = cure rate and egg reduction rate of 40-59%; ++ = cure rate and egg reduction rate of 20-39%; + = cure rate and egg reduction rate of 0-19%. [b]Not recommended for pregnant women or children. [c]*A. duodenale* and *N. americanus*.

Table 6. Frequently recommended oral dosage of drugs against soil-transmitted helminthiasis.

Drug	Recommended oral dose	Source
Albendazole	400 mg single dose for 1-3 days (children aged 1-2 years 200 mg)	83,85,87
Diethylcarbamazine	100 mg for 2-5 year old, 200 mg for 6-15 year old, 300 mg for >15 year old	83
Ivermectin	200 µg/kg single dose for 1-2 days	85,89
Levamisole	2.5 mg/kg single dose	83,85,87
Mebendazole	500 mg single dose	83,85,87
Piperazine	75 mg/kg single dose	85
Pyrantel pamoate	10-40 mg/kg single dose for 1-3 days	83,85,87
Tribendimidine	Various doses: 200 mg/kg to 400 mg/kg single dose for 1-3 days	85

As illustrated by Table 5, the armoury against ascariasis contains several highly efficacious drugs, whereas the situation is less satisfactory with regard to hookworm infections and even worse with regard to trichuriasis. Currently, albendazole and mebendazole are the recommended treatment by WHO against ascariasis, hookworm infection, and trichuriasis, and hence also the most widely used drugs.[13,14,83,87] As with schistosomiasis, adjuvant therapy may be needed in case of severe complications and/or sequelae.[13] One tablet of 400 mg albendazole or 500 mg mebendazole costs as little as US$ 0.02 and donations made by the pharmaceutical industry included also drugs against soil-transmitted helminthiasis.[33,83,84]

1.6. Control of schistosomiasis and soil-transmitted helminthiasis

Due to many common features, this chapter combines the discussion pertaining to the control of schistosomiasis and soil-transmitted helminthiasis. This is in line with growing efforts for integrated control of multiple NTDs.[33,73,92,93]

As described in the previous chapters, schistosomiasis and soil-transmitted helminthiasis mainly affect developing countries in the tropics and particularly poor rural communities. High intensity or long-standing infections lead to a variety of sequelae and negatively impact on pregnancy and birth outcome, cognitive and physical development, and work capacity, thus draining the social and economic development of affected communities.[1,94,95] The awareness of this vicious cycle and the availability of efficacious, safe, affordable and easy to use drugs resulted in a control strategy phrased “preventive chemotherapy”.[12] Preventive chemotherapy means the regular untargeted or targeted drug administration to populations considered at-risk of morbidity without prior diagnosis and with the primary objective to control morbidity and transmission.[12,83,96] This strategy of helminth control through large-

scale administration of chemotherapy was endorsed by WHO in the mid-1980s[25,33,97-99] and gained further momentum at the beginning of the new millennium as the World Health Assembly (WHA) resolution 54.19 urged member states to treat at least 75% and up to 100% of all school-aged children and other high-risk groups with praziquantel against schistosomiasis and albendazole or mebendazole against soil-transmitted helminthiasis.[33,73,84] Following current WHO guidelines, all schoolchildren and high-risk groups should be treated once or twice every year in high prevalence communities (≥50%) and once or twice every two years in moderate prevalence communities (10-50%). In low prevalence communities (<10%), chemotherapy should be made available through health facilities for the treatment of suspected cases.[83] Experience with preventive chemotherapy suggests that this strategy, implemented in highly endemic areas, indeed effectively reduces morbidity.[33,100,101]

However, preventive chemotherapy raises several issues that must be considered. For instance, the potential development of resistance to widely and repeatedly administered anthelminthic drugs necessitates careful monitoring to duly recognize treatment failures. Of note, anthelminthic drug resistance is already a major issue in veterinary public health, where drugs are applied on a large scale with very high coverage rates.[41,102-111] Despite ongoing efforts, there are currently no vaccines available against schistosomiasis and soil-transmitted helminthiasis and vaccines may only become part of a solution in the future.[1,112,113] Hence, the need for the development of novel anthelminthic drugs and innovative approaches to prolong the useful lifespan of existing drugs, such as their alternating or combined use, have been emphasized.[41,85-87] Thus far, no indications for severe negative pharmacokinetic interactions or limitations due to decreased safety and tolerability have been reported with regard to tested combinations of drugs listed in Table 3 and Table 5.[85,86,88,90,91] Interestingly though, while some combinations of drugs with different modes of action showed efficacies that were comparable to single drug treatments, other combinations such as praziquantel plus artesunate against *S. haematobium* and *S. mansoni*,[85,86] mebendazole plus levamisole against hookworm,[85] and albendazole or mebendazole plus ivermectin against *T. trichiura*[85,88,90] revealed higher cure and/or egg reduction rates.

In order to reinforce and consolidate achievements made by preventive chemotherapy, and to lower the dependency from chemotherapy, more integrated approaches, including improved sanitation, education and, particularly for schistosomiasis, intermediate host snail control are of pivotal importance.[5,13,41,114] Improved sanitation mainly consists of toilets and latrines that ensure the hygienic disposal of human excreta and access to clean water that permits safe recreational and occupational usage (e.g., bathing, fishing, watering, washing,

drinking and cooking).[31,32,41,115,116] A promising approach to reduce the faecal contamination of the environment is community-led total sanitation (CLTS), for instance.[117,118] Health education – or better interactive health communication – is essential to inform, motivate, encourage and train people, to receive feedback from them, and to ensure continuing participation, self-reliance and, if need be, behavior change.[31,34,119,120] Intermediate host snail control as part of an integrated control approach against schistosomiasis is mainly based on the use of molluscicides and to some extent on environmental management.[5,28]

Improved sanitation, education and intermediate host snail control aim at interrupting the parasite's life cycle and therefore the control of transmission. Interestingly, transmission control was the recommended strategy to fight schistosomiasis until the mid-1980s. However, with the advent of safe and efficacious drugs (e.g., praziquantel), the emphasis shifted from transmission to morbidity control.[5,13,41,73,114,121] Nowadays, control plans envisage morbidity control in highly endemic settings and with decreasing endemicity prevalence control, transmission control and, ultimately, surveillance and detection of the few remaining cases in order to eliminate the diseases (Figure 5).[73,100] There is broad consensus that avoiding severe morbidity should be the first priority in high-endemicity settings.[83,100] At this early stage, the identification of such high-endemicity areas is more important than exact individual diagnosis and preventive chemotherapy with the current arsenal of available cheap and safe drugs indeed prevents from most severe sequelae.[73,83,100] Once the initial efforts successfully reduced morbidity and partially also prevalence and transmission, cost-effectiveness and sustainability of the continuation becomes essential.[33,100] Screening and treatment strategies have to be adjusted to the changing epidemiological situation.[122,123] With decreasing number of infected individuals, more targeted treatment is likely to become more cost-effective than continued large-scale drug administration,[124] but asks for increasing accuracy of diagnostics.[73] Furthermore, while vertical programs may be initially successful, they should be carefully absorbed into more horizontal sector-wide and intersectoral approaches.[12,114,125-130] However, the appropriate mix and timing of interventions, diagnostics and governance depend on the characteristics of the targeted helminth species and location and have been at the root of many fervent debates, including the question whether continued drug-based interventions could push transmission even below a "transmission breakpoint" and thereby reaching elimination on its own without ever being supported by additional interventions.[96]

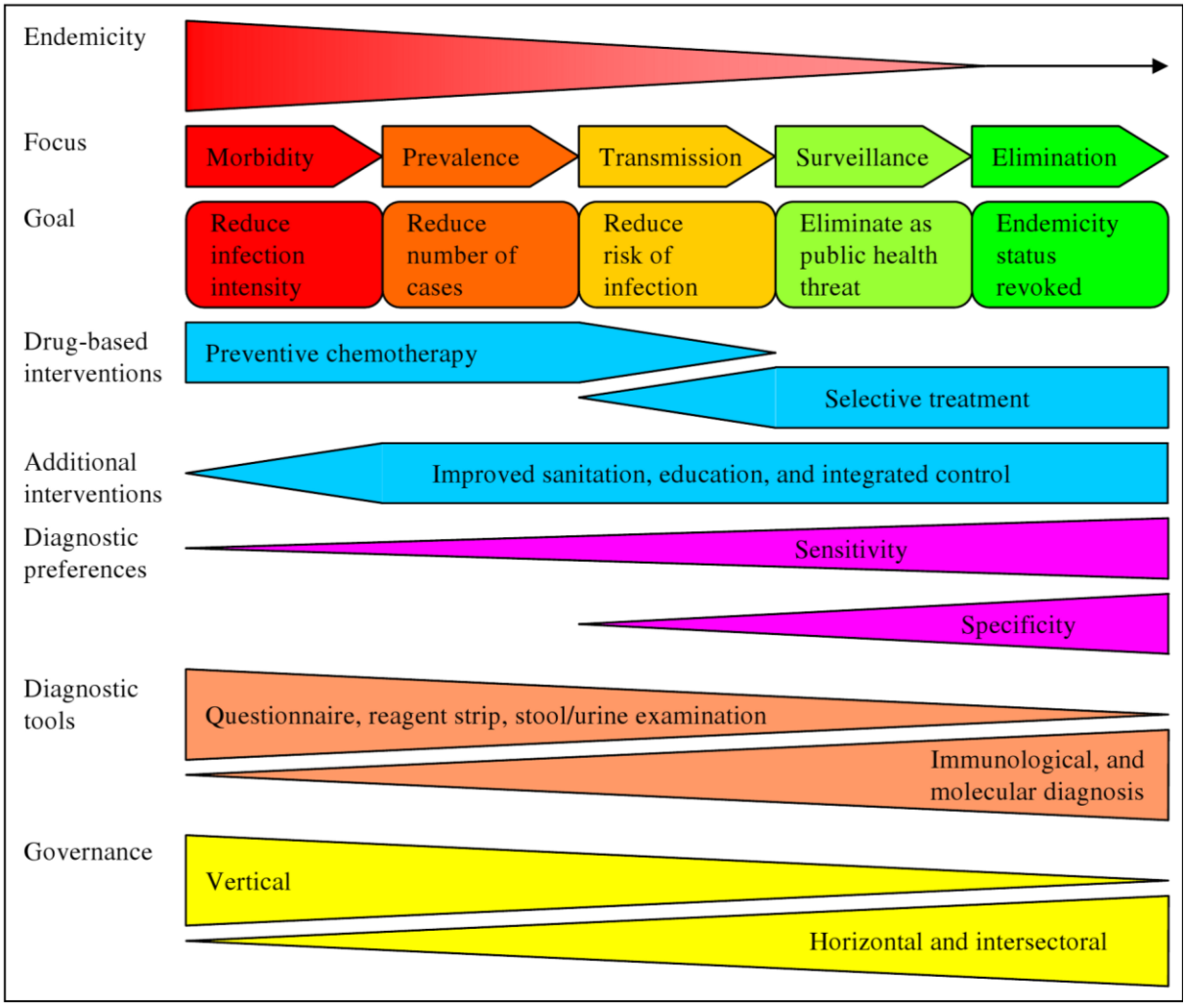

Figure 5. Schematic illustration of how falling endemicity levels influence helminth control programs. This figure has been further developed based on references [73,96,100].

Over the past years, disease mapping and modeling by using geographical information systems (GIS) and remote sensing became important tools in control programs and demonstrated considerable geographical overlaps of different NTDs.[1,9,40,113] Furthermore, as the NTDs share certain risk factors, concurrent infections with multiple parasite species are often the norm rather than the exception.[20] Awareness of these facts, the availability of drugs, which act against several of the causative agents simultaneously or can be safely combined, and cost-effectiveness considerations led to the quest for the integration of NTD control programs.[1,9,113]

1.7. Assessing human health on a global scale

1.7.1. Why is it important to assess human health on a global scale?

Having valid, reliable and comparable data is a precondition for the most effective use of scarce resources. This is important for donors, decision makers and health program managers at the one end of the public health system, but even more important for those in need at the other end of the system.[131] Hence, evidence on the magnitude and distribution of the global burden of disease and its trends over time are a critical input to well-informed decision making at all levels.[132] In an increasingly globalized world with new, powerful players in the public health sector (e.g., Bill & Melinda Gates Foundation) and increasingly globalized target-setting (e.g., the United Nation's (UN) millennium development goals (MDGs)), decisions on the global level are an important factor and need to be governed by global evidence.

Unfortunately, descriptive epidemiology and health measurement at the population level may not be sufficiently novel for major funding bodies, other investigators, and journal audiences, and are therefore underrepresented in the epidemiological literature.[132,133] Traditional epidemiological journals tended to concentrate on causal and quasi-experimental studies over the past years and cross-disciplinary debate became increasingly fragmented. Hence, there is a need for increased efforts in population health measurement, which could also bridge a range of currently disjoint fields relating to health such as medicine, biology, epidemiology, demography, health economics and broader social science disciplines.[133]

1.7.2. Definition and historical background of the DALY concept

The assessment of human health on a global scale made a big step forward in the late 1980s and early 1990, when WHO and the World Bank developed the DALY concept, as a new, scalable, time-based measuring unit for quantifying the health burdens caused by different diseases and injuries.[132] The DALY is a time-based measure that combines years of life lost (YLLs) and years lived with disability (YLDs).[134] Hence, it does not directly measure health, but rather the loss of healthy life by combining the burden of fatal with that of non-fatal conditions. In economic terms, they are a "bad" which should be minimized. In this sense, the terminology of DALY can be misleading as more of a "life year", even when "adjusted", should be a good and therefore maximized and not minimized.[135]

Simplified, the burden for a particular health state as expressed in DALYs is computed as follows:

DALYs = Σ YLLs + Σ YLDs,

with YLLs from a single death equal to (standard life expectation - age at death) * (age weight) * (future discount)

and YLDs from a certain disabling condition equal to (disability weight) * (incidence) * (duration of disabling event) * (age weight) * (future discount).

The first global burden of diseases study commenced in 1992. The study was based on the DALY concept and had the following three major objectives:

(i) to facilitate the inclusion of non-fatal health outcomes;

(ii) to decouple epidemiological assessment from advocacy so that estimates are as objective as possible; and

(iii) to quantify the burden of disease using a measure that could also be used for cost-effectiveness analysis.[136]

It provided the first comprehensive, consistent and comparable set of DALY estimates for 107 diseases and injuries and 10 selected risk factors. Results were stratified by age, sex and the eight world regions (those used by the World Bank at the time) and reported for the year 1990 with projections made for the year 2020.[134,137]

After the original global burden of disease study, work continued to improve the methods[138-141] and to analyze additional and newly acquired data.[142] Between 1999 and 2004, WHO published annual global burden of disease estimates in the annex tables of the World Health Report.[143-148] The global burden of disease results also provided a framework for the disease control priorities project (DCPP), which focused on cost-effectiveness and priority setting analysis.[149] New estimates for 136 diseases and injuries and 19 risk factors for eight different world regions in the year 2001 were published in 2006.[150] The global burden of diseases 2001 study included newly available data, but some burden of disease estimates and most disability weights used for calculation continued to rely on the original work done in 1990.[132]

In 2007, the first complete systematic revision of the original global burden of diseases 1990 study was launched. Its goal is to (re-)evaluate the global burden of 175 diseases and injuries (based on ICD-10 codes) and 43 risk factors for 21 regions of the world in 1990 and 2005.[132,134,151] Postponed several times, final results of this major update and overhaul are

now scheduled for publication in summer 2012. Indeed, the final study results will incorporate a complete (re-)assessment of all available primary data sources and harness all methodological improvements achieved over the past years. Amongst other issues, new disability weights for an updated list of sequelae will be derived and attempts are made to further decouple the initial disability weights from pure expert elicitation.[132,134,151]

1.7.3. Critical appraisal of previous global burden of disease studies

An undeniable merit of the global burden of disease concept is the renewed interest in descriptive epidemiology and population health measurement. It has stimulated a controversy that circled around three main topics. First and foremost, criticism focused on the construction of the DALY metrics[132] and the determination of age-specific weights, future discounting and disability weights.[135,136,152-157] Of particular interest for the present PhD thesis, the original disability weights, which should capture the disability incurred by an average case suffering from a certain condition in percentages, were solely based on expert opinion.[136] As a second main point of criticism, concerns have been raised about the desirability and implications of extrapolation of population health estimates where basic descriptive epidemiological data are limited, uncertain or even missing.[132,158,159] As a third main point of criticism, some health economists have argued that the global burden of disease analyses do not help in setting health priorities. They were afraid that future priority setting could be based only on the magnitude of disease burdens, whereas the marginal cost-effectiveness of potential interventions, in their eyes the crucial parameter, could be ignored.[153,160] Also, they highlighted some consequences which run against equity principles if DALY minimization becomes the most important criterion.[135,161]

The ongoing debate about the most accurate way to evaluate the global burden of diseases as well as discussions about the best organizational structure for data compilation[162] also reflect the political power of such statistics. The fervent pleas of a wide range of interest groups to (re-)evaluate certain disease burden calculations[11,152,163-165] or the partial or complete refusal of the DALY concept mainly due to “ethical” reservations point in the same direction.[156,166,167]

1.7.4. Parasitic infections in the tropics: the "big three" and the NTDs

In 2004 the global burden of disease was estimated to be over 1.5 billion DALYs lost. Approximately 60% of this burden was due to YLLs and 40% to YLDs.[168] Among the 10 leading diseases and conditions in terms of global burden were a number of diseases that are particularly widespread in the developing world, namely perinatal conditions, lower respiratory tract infections, HIV/AIDS, diarrhoeal diseases, malaria and tuberculosis.[158] Africa is the continent with the highest disease burden per person of all world regions. Indeed, while only 11.5% of the world's population live in Africa, almost one quarter (24.7%) of the global burden is concentrated there. This high burden is predominantly due to group I conditions (communicable diseases, maternal, perinatal and nutritional conditions), which comprise all the aforementioned diseases. According to these figures, 44.3% of the global burden of group I conditions and even 52.9% of the global burden of infectious and parasitic diseases occur in Africa.[168]

Thus far, most control efforts addressed the three most devastating diseases in developing countries, i.e., HIV/AIDS, tuberculosis and malaria, which, together, account for a staggering 166 million DALYs.[1] Considerable progress has been made in the control of these "big three" diseases, but success has been uneven.[169,170] Indeed, analysis for Africa indicate that the UN's MDGs will not be achieved in 2015 at the current rates of improvement for most indicators.[171] In general, differences in morbidity and mortality among different world regions are still large and have even widened over the past years.[172,173]

Less attention has been paid to the NTDs, which include a number of helminth infections (e.g., schistosomiasis, soil-transmitted helminthiasis, lymphatic filariasis and food-borne trematodiasis), vector-borne protozoan infections (e.g., human African trypanosomiasis), and certain bacterial infections (e.g., Buruli ulcer and trachoma). Estimates for the global burden of all NTDs together are as high as 56.6 million DALYs, which is in the range of each of the "big three".[1,174] Effective treatment and prevention strategies are available for several of the NTDs for less than US$ 1 per capita per year. New evidence indicates substantial geographical overlap between some NTDs and the "big three", co-morbidity seems common and treatment and control of NTDs might also positively affect the progression of the "big three".[1,113,125,174,175] Nevertheless, NTDs are often disregarded because their primary impact is on the poorest of the poor and their public health, economic and societal impact is still underestimated.[1,125,152,174]

It is important to note, however, that large uncertainties are attached to current burden estimates. This prevailing ambiguity is partially explained by the lack of general vital

registration and cause-of-death statistics across large parts of the developing world[131,176,177] and partially by systematic problems in the DALY construction.[132,152,178]

1.8. Assessing human health on a local scale: why is it important?

The importance of assessing human health on a local scale can be justified on at least three grounds. First, it is important to eliminate the "scandal of invisibility" and make "everyone count by counting everyone".[131] The roots of this scandal of invisibility are the absence of reliable data for births, deaths and causes of deaths, i.e., vital statistics. Civil registration, as the most efficient tool for generating vital statistics, is the only means of establishing and protecting identities, citizenship and property rights. Visibility demands accountability, which in turn generates the ability to count. Unregistered people remain unseen.[131] This does not only apply to vital events, but also to morbidity due to diseases and injuries. The awareness for certain health problems can be raised only if cases are noticed and properly registered.

Second, precise information of human health on a local scale are the foundation of the global summary measures. The more accurate and comprehensive they are, the more precise the resulting global estimates. Otherwise, we would have "uncertain inputs multiplied by uncertain weights (which) yield estimates that are even more uncertain".[159] Unfortunately, the limitations of available data often resulted in the use of expert opinion.[132] Current research demonstrates the feasibility of filling the gap by generating high-precision community-based data instead of expert opinion.[163] Further efforts specifically designed to detect incidence rates, disability weights and transition rates, among others, could follow a standardized protocol and generate crucial data. Furthermore, existing large-scale demographic and epidemiological data, which are collected in the frame of population surveillance projects (e.g., the International Network for the Continuous Demographic Evaluation of Populations and their Health in Developing Countries (INDEPTH network)) may also help to fill existing gaps.[165]

Third, assessing human health on a local scale is crucial to any intervention such as disease control programs. The most appropriate approach for the identification of those in need and for monitoring progress made may change over the lifespan of a control program. Hence, the development of rapid, inexpensive, simple and culturally adapted diagnostic approaches at each stage of a control programs received increasing attention since the late 1980s.[72] Particularly for morbidity and prevalence control, simple anamnestic questionnaire tools were developed and widely used in programs against urinary schistosomiasis by asking

people whether they had "blood in urine" (haematuria) over the past 2-4 weeks.[72,179-183] The questionnaires have also been adapted for the screening of *S. mansoni*[72,179,184-188] and *S. japonicum*.[189,190] They included questions about signs, symptoms, and/or risk factors and were intended for the identification of high-risk communities (for public health) or individuals (for clinical practice). Thus far, their application revealed satisfactory diagnostic performance in the screening for *S. haematobium* and *S. japonicum*, but only moderate accuracy for *S. mansoni*[189,191] and their adaptation for additional helminthic infections was considered challenging.[73,192] Consequentially, additional efforts are needed to verify the true potential and limitations of anamnestic questionnaires.

1.9. References

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2. Identified research needs

2.1. Identified research needs

There is a lack of health-related data, particularly in developing countries,[1-5] where most of the NTDs prevail and mainly affect the poorest of the poor.[6-9] NTDs predominantly cause disability and not death[6,7,10] and morbidity is more difficult to measure than mortality as there are different levels or "intensities" of morbidity (i.e., disability, as tentatively measured in the disability weights in the global burden of disease studies) but not of mortality (i.e., death). Hence, uncertainties in morbidity assessments tend to be even higher than in mortality assessments.[11] All these facts contribute to the reality that the public health and socio-economic significance of NTDs are often underestimated. Consequently, there is a lack of coordinated research and control efforts directed towards these diseases.[6-9]

Among the many issues raised, we decided to focus on the assessment of morbidity and burden caused by NTDs. In order to raise the profile of the NTDs, and hence to come closer to realistic estimates and an appropriate handling of the problem, there is an urgent need for a more comprehensive, credible and critical morbidity assessment of this group of diseases at all geographical levels. On a global scale, it is important "to explicitly address additional diseases not currently included in the global burden of diseases study".[3] Of particular interest here, food-borne trematode infections constitute such a widely neglected cluster of diseases.

In addition, the list of sequelae and disability weights associated to NTDs in burden calculations warrant further scientific inquiry by including also population-based evidence and addressing the issues of subtle morbidity, age- and sex-specificity, chronic infection and co-infection, which are the norm rather than the exception for the NTDs.[3,7,8,10,12-14] This second point would also help to bridge the gap between more theoretical, global contemplations and real survey data from the field.

Finally, as detailed in the introduction, reliable and efficient methods for the identification of individuals and communities in need of treatment are key to sustainable and cost-efficient disease control programs. Simple anamnestic questionnaires are considered as rapid and inexpensive screening techniques in the field in order to guide local morbidity and infection control. Hence, new research should verify whether the existing questionnaire tools can be further refined and their usefulness extended over the course of control programs, i.e., when prevalence rates and infection intensities begin to decline or are already low (Figure 5).[15]

Moreover, the usefulness of combined questionnaire approaches, which aim not only at single species but also broader (anthelminthic) treatment groups should be explored.

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3. Goal and specific objectives

3.1. Goal

The goal of this PhD thesis was to develop, validate, and apply tools for assessing the morbidity and burden caused by different NTDs at different geographical scales.

3.2. Specific objectives

The following three specific and interrelated objectives were pursued in order to achieve this goal:

Objective 1: To participate in the global burden of diseases, injuries and risk factors study 2010 and assess – for the first time ever – the global burden of human food-borne trematodiasis following study guidelines.

Objective 2: To generate new evidence on the disability incurred by individuals infected with schistosomes and/or soil-transmitted helminths in field-based epidemiological investigations and compare the results with the most recent disability weights of the global burden of disease study.

Objective 3: To explore the potential of simple and low-cost anamnestic questionnaire tools for the assessment of morbidity due to schistosomiasis and soil-transmitted helminthiasis in the recently established Taabo health demographic surveillance site (HDSS) in Côte d'Ivoire in order to identify high-risk groups and guide control measures.

The present PhD thesis included different NTDs and combined theoretical desktop work on the global scale (objective 1) with practical field work on the spot (objectives 2 and 3). The different geographical scales as well as desktop and field work were seen as complements, which fruitfully stimulate each other. The overarching goal, the three specific objectives, the different geographical scales, the methods, and the different NTDs considered in this thesis are summarized in the theoretical framework depicted in Figure 6.

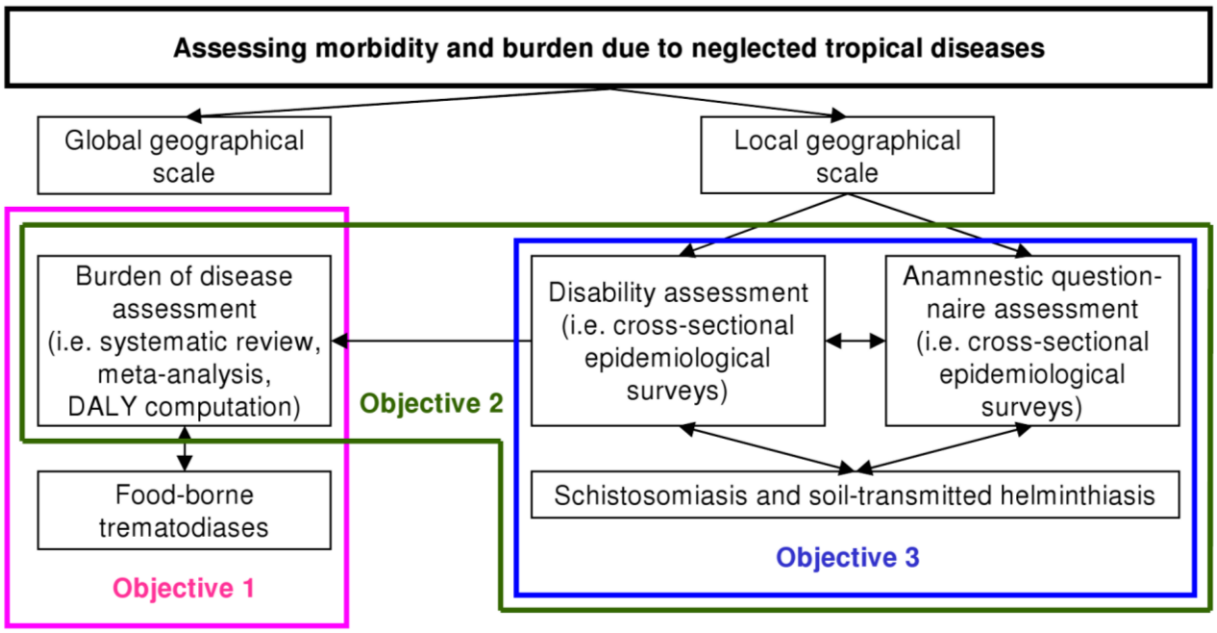

Figure 6. Theoretical framework of the present PhD thesis. The framework highlights the goal, objectives, different geographical scales, methods, and neglected tropical diseases considered in the present PhD thesis.

4. Study sites

4.1. Study sites

The field work of the present study took place in two sites in south and south-central Côte d'Ivoire (Figure 7). A first cross-sectional survey was carried out in early 2010 in Grand Moutcho, a village just 3 km outside Agboville, which is the capital city of the equally named district. Grand Moutcho is located in the valley of the Agnéby River approximately 80 km north of Abidjan. The region is at the interface of the tropical rainforest zone in the south and the savannah zone in the north. The tropical climate follows a seasonal pattern with a dry season between November and April and one to two rainy season between May and October. Schistosomiasis and soil-transmitted helminthiasis are endemic in the area.[1-3] People are mainly engaged in subsistence farming.

Additional cross-sectional surveys were carried out in mid-2010 and mid-2011 in the Taabo health demographic surveillance system (HDSS). The Taabo HDSS is the first of its kind in Côte d'Ivoire and was established in 2008 by the following partners: the Unité de Formation et de Recherche (UFR) Biosciences, Université de Cocody (Abidjan, Côte d'Ivoire), the Centre Suisse de Recherches Scientifiques en Côte d'Ivoire (CSRS; Abidjan, Côte d'Ivoire), the Health District of Tiassalé, Sous-Préfecture de Taabo (Tiassalé and Taabo Cité, Côte d'Ivoire), the Swiss Tropical and Public Health Institute (Swiss TPH; Basel, Switzerland) and Fairmed (Bern, Switzerland). The 2-year start-up funding was provided by the Swiss non-profit organization Fairmed.[4] Standard methodologies for demographic surveillance were implemented according to the INDEPTH network.[5]

The Taabo HDSS covers most of the rural Sous-Préfecture de Taabo. Its main station is located in Taabo Cité, the only small urban center belonging to the Taabo HDSS, some 160 km north-west of Abidjan. The area's vegetation and climate are similar to those of the Agboville region. The Bandama River is running through the area and has been dammed up in the late 1970s for hydroelectric power generation.[6] Neglected tropical diseases[6-9] and malaria[10] are highly endemic in the area and the understanding of transmission dynamics and associated morbidity and integrated control measures to reduce the burden of these diseases are specific aims of the Taabo HDSS.

About 38,500 individuals in 6,400 households are under longitudinal demographic and health surveillance in the Taabo HDSS. Approximately one fifth of the households reside in Taabo Cité, another three fifths in 13 main villages, and the remaining fifth in more or less

remote hamlets. People are mainly engaged in subsistence farming of yams, banana and manioc, with limited cash crop production of coffee and cacao. Furthermore, there are some artisans, some fishermen around Lake Taabo and some shopkeepers and businessmen mainly in Taabo Cité (Taabo HDSS, unpublished data).

Figure 7. Study sites. The field work of the present thesis took place in Grand Moutcho (early 2010) and the Taabo HDSS (mid-2010 and mid-2011), south and south-central Côte d'Ivoire. (Adapted from: http://www.lib.utexas.edu/maps/africa/cote_divoire_rel04.jpg).

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5. Clinical review: manifestation, diagnosis, and management of food-borne trematodiasis

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Summary points.

Food-borne trematodiasis is a cluster of zoonotic infections caused by parasitic trematodes ingested in undercooked, mainly aquatic, food

Prevalence is increasing because of the growth of inland fish production; most cases are in Asia and Latin America, but infections in migrants and returning travellers are reported elsewhere, including Europe and North America

Food-borne trematodes are grouped as liver, lung, and intestinal flukes and—depending on the species, the duration and intensity of infection, and host susceptibility—inflammatory lesions and damage to tissues and organs occur with various clinical manifestations

The most serious clinical consequences are cancer of the bile duct (in clonorchiasis and opisthorchiasis) and ectopic infections (mainly in paragonimiasis, but also in fascioliasis and intestinal fluke infections)

Direct parasitological diagnosis via the detection of eggs in faeces (all flukes) and sputum (lung flukes only) is the most common approach

Praziquantel and triclabendazole are safe and efficacious treatments but other drugs are being investigated

Sources and selection criteria for included information.

Information for this clinical review was obtained from a database that we established for a project to estimate the global burden of food-borne trematodiasis.[2] The database originated from a systematic review of 11 electronic datasources: PubMed, WHOLIS, FAOBIB, Embase, CAB Abstracts, LILACS, ISI Web of Science, BIOSIS Preview, Science Direct, African Journals Online, and SIGLE. It included all available literature from 1 January 1980 to 31 December 2008 and had no language restrictions. Details on the initial search strategy and database have been presented elsewhere.[2] For this review, the database was updated to include all available information until 30 September 2011. The data were complemented by personal reference archives and the authors' experience.

Food-borne trematodiasis is a cluster of zoonotic infections caused by parasitic worms (class: trematoda; also known as flukes), which are transmitted via the ingestion of contaminated, mainly aquatic, food. More than one billion people are at risk of infection according to a systematic review from 2005.[1] Another systematic review and meta-analysis suggests that 56 million people were infected in 2005, mainly in Asia and Latin America, with a global burden of 665,000 disability adjusted life years.[2]

Depending on the fluke species, food-borne trematodiasis is associated with a variety of signs, symptoms, and pathological consequences. The non-specificity of the clinical manifestations, the wide range of fluke species, and shortcomings in current diagnostic techniques are some of the reasons why food-borne trematodiasis is underestimated.[3,4]

This review introduces the most important food-borne trematode species and describes their geographical distribution. It also discusses pathological consequences, clinical manifestations, diagnosis, treatment, and control of food-borne trematodiasis. Our review is based on the limited evidence obtained from the peer reviewed literature, textbooks, reports, and international guidelines.

5.1. What causes food-borne trematodiasis?

A recent systematic review listed more than 80 different trematode species that have been identified from human infections.[2] According to the target organ in the definitive host, they are grouped as liver, lung, or intestinal flukes. However, on the basis of recent biomedical reviews and still incomplete national prevalence data, only a dozen species are of public health importance (Box 1).[2,5-8]

Box 1. Food-borne trematode species of public health importance.

Liver flukes: *Clonorchis sinensis, Opisthorchis felineus, O. viverrini, Fasciola gigantica, F. hepatica*

Lung flukes: *Paragonimus* spp.

Intestinal flukes: *Echinostoma* spp., *Fasciolopsis buski, Gymnophalloides seoi, Haplorchis* spp., *Heterophyes* spp., *Metagonimus* spp.

The life cycles of the food-borne trematodes are species specific, with distinct snail species being first intermediate hosts, and fish, mollusc, crustacean, amphibian, and insect species being second intermediate hosts (Figure 8). Notable exceptions are *Fasciola* spp. and *F. buski*, which do not need a second intermediate host, as their infectious stages (so called metacercariae) adhere directly to aquatic plants.[3] A detailed list of known first and second intermediate hosts can be found in the annex of a comprehensive technical report published by the World Health Organization.[9]

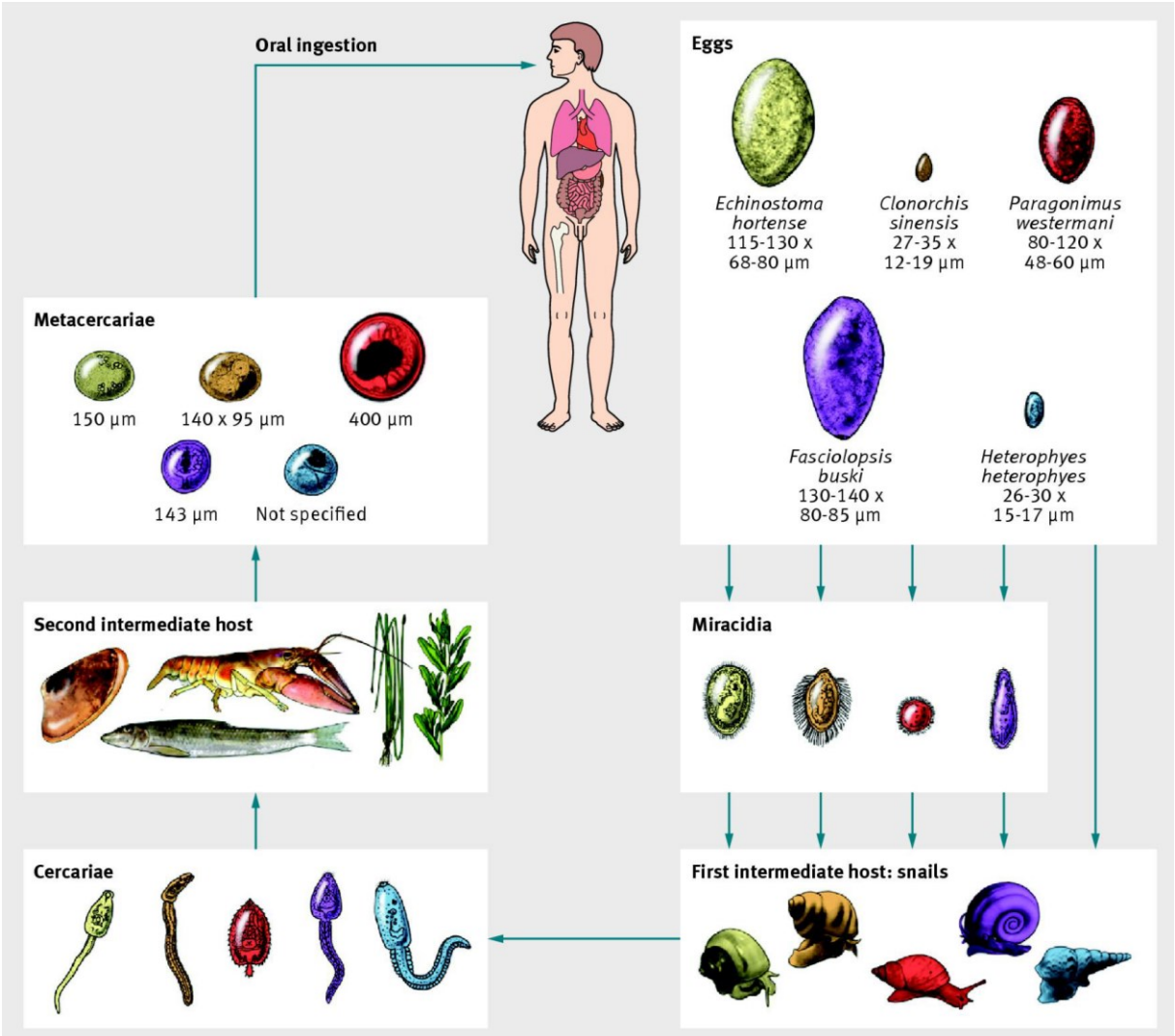

Figure 8. Representative life cycles of five food-borne trematodes – a liver fluke (*Clonorchis sinensis*), a lung fluke (*Paragonimus westermani*), and three intestinal flukes (*Echinostoma hortense*, *Fasciolopsis buski*, and *Heterophyes heterophyes*). Adapted from Keiser and Utzinger,[3] with permission from the American Society for Microbiology.

Humans usually acquire an infection through the ingestion of second intermediate hosts or, in the case of *Fasciola* spp. and *F. buski*, aquatic plants that contain viable metacercariae. With the exception of *Fasciola* spp. and *F. buski*, metacercariae are not released from their intermediate hosts into water, so the risk of infection from drinking untreated water is small.[9,10] It is unclear which aspects of food processing (such as heating, freezing, smoking, acidification, salting, drying, washing, disinfection, irradiation, and pressure treatment) inhibit the infectivity of metacercariae, but properly cooked or deeply frozen food is considered safe.[9,11] In the duodenum of an infected human, hermaphroditic juvenile flukes develop from the metacercariae, migrate to their target organ, mature, mate, and start producing eggs. Parasite eggs are then released via the human host's faeces (all food-borne trematodes, including coughed up and swallowed eggs of *Paragonimus* spp.) or sputum (only coughed up eggs of *Paragonimus* spp.) and have to reach appropriate water bodies with suitable intermediate hosts to complete their life cycles.[3,12]

5.2. Where does food-borne trematodiasis occur?

Food-borne trematodiasis is commonly classified as a tropical disease, even though the endemic area is not limited to the tropics.[9,11] *C. sinensis* is endemic in East and South East Asia; *O. viverrini* in South East Asia; and *O. felineus* in central, northern, and western Eurasia. *Fasciola* spp. exist worldwide, but most endemic areas are in the Andean region, North Africa, and the Caspian Sea region. *Paragonimus* spp. occur in parts of the Andean region, West and Central Africa, East and South East Asia, and North America. Intestinal flukes are found worldwide, with most endemic areas in East and South East Asia. A comprehensive literature review identified allochthonous cases (diagnosed in countries where disease transmission does not naturally occur) all over the world, probably as a result of increasing international travel, human migration, and the food trade.[13] A series of recent reviews suggests that human food-borne trematodiasis is increasing, mainly because of the exponential growth of inland fish production (aquaculture).[1,2,9,11,w1,w2]

At a regional level, food-borne trematodiasis usually shows a focal distribution, which is governed by social-ecological contexts (such as specific eating habits and environmental conditions that favour maintaining the parasites' life cycles).[3,11] At the individual level, a meta-analysis of the proportion of infected humans shedding high numbers of eggs indicates that distribution is highly aggregated: a few people harbour most of the parasites.[2] Hospital based and community based cross sectional surveys in endemic areas show that infection with

multiple species of food-borne trematodes is common because they are all acquired through consumption of raw food.[14,w3,w4]

5.3. What are the pathological consequences and clinical manifestations?

Morbidity depends on the species involved and also the host's susceptibility, duration of infection, and the number of worms harboured (infection intensity). These parameters govern the occurrence and severity of inflammatory lesions and damage to tissues and target organs. The severity of infection is usually determined by the number of parasite eggs per gram of faeces or per 5 mL of sputum in paragonimiasis.[3-9,11,15-17,w5-w19] Because the egg laying capacity of food-borne trematodes varies greatly – from fewer than 100 eggs per day per worm (*Haplorchis taichui*)[18] to 13,000-26,000 (*F. buski*)[19] – species specific thresholds are used to differentiate between light, moderate, and heavy infections. However, these thresholds have never been standardised. Furthermore, some studies challenge a direct association between egg counts and worm burden because crowding effects may lower egg production, obstructions in the hosts' organs may affect the excretion of eggs, and the distribution of eggs in faeces can be uneven.[15,16,20,w20-w24]

5.3.1. Clonorchiasis and opisthorchiasis

The pathological consequences and clinical manifestations of infection with *C. sinensis* and *Opisthorchis* spp. are similar. After ingestion by the host, the metacercariae excyst in gastric juice and migrate via the duodenum, the ampulla of Vater, and the extrahepatic biliary system to the intrahepatic bile ducts.[11] Pathological changes are mainly confined to the bile duct, liver, and gallbladder.[7] Tissue damage is caused directly by the parasite via mechanical and chemical irritation and indirectly via the immune response, and it can lead to cancer of the bile duct (cholangiocarcinoma; Box 2).[11,21] Hepatomegaly, gallbladder enlargement, gallstones, sludge, and periductal fibrosis along the intrahepatic biliary tree and periportal vein are often seen with ultrasonography (Figure 9 and Figure 10).[4]

Acute and light infections are mostly asymptomatic,[3,9,11,21] but an acute onset with hepatitis-like symptoms, including high fever and chills, has been reported, particularly for infection with *O. felineus*.[3,7,11,w25] Some moderately infected people may have mild symptoms,[3,21,w8] but even chronic infections may remain asymptomatic, and often only heavily infected people have symptoms, signs, and complications (Table 7).[3,7,9,11,21]

Box 2. Liver fluke induced cholangiocarcinoma.

Pathological consequences and clinical manifestations: Cholangiocarcinoma is a malignant tumour of the bile duct epithelium. Although the exact mechanism of liver fluke induced carcinogenesis is unclear, chronic biliary infection increases the susceptibility of the bile ducts to the action of carcinogens. Patients usually present with non-specific symptoms, which are similar to those of liver fluke infections. Liver fluke induced cholangiocarcinoma cannot be differentiated from other forms of cholangiocarcinoma. Timely diagnosis is rare and prognosis is poor, even when patients receive appropriate treatment.

Diagnosis: The diagnosis, localisation, and staging of cholangiocarcinoma are challenging and require a combination of imaging, biochemical investigations, and cytological techniques (ultrasonography, cholangiography, choledochoscopy, computed tomography, positron emission tomography, magnetic resonance imaging, biopsy and cytological analysis, and laboratory analysis of serum tumour markers).

Management: Consultation with an infectious disease specialist, hepatologist, and oncologist is recommended. Response to chemotherapy is poor. Complete resection with negative histological margins or transplantation are the only curative interventions. Currently, no effective adjuvant treatment exists, but radiotherapy may be indicated postoperatively. Often, only palliative treatment remains.

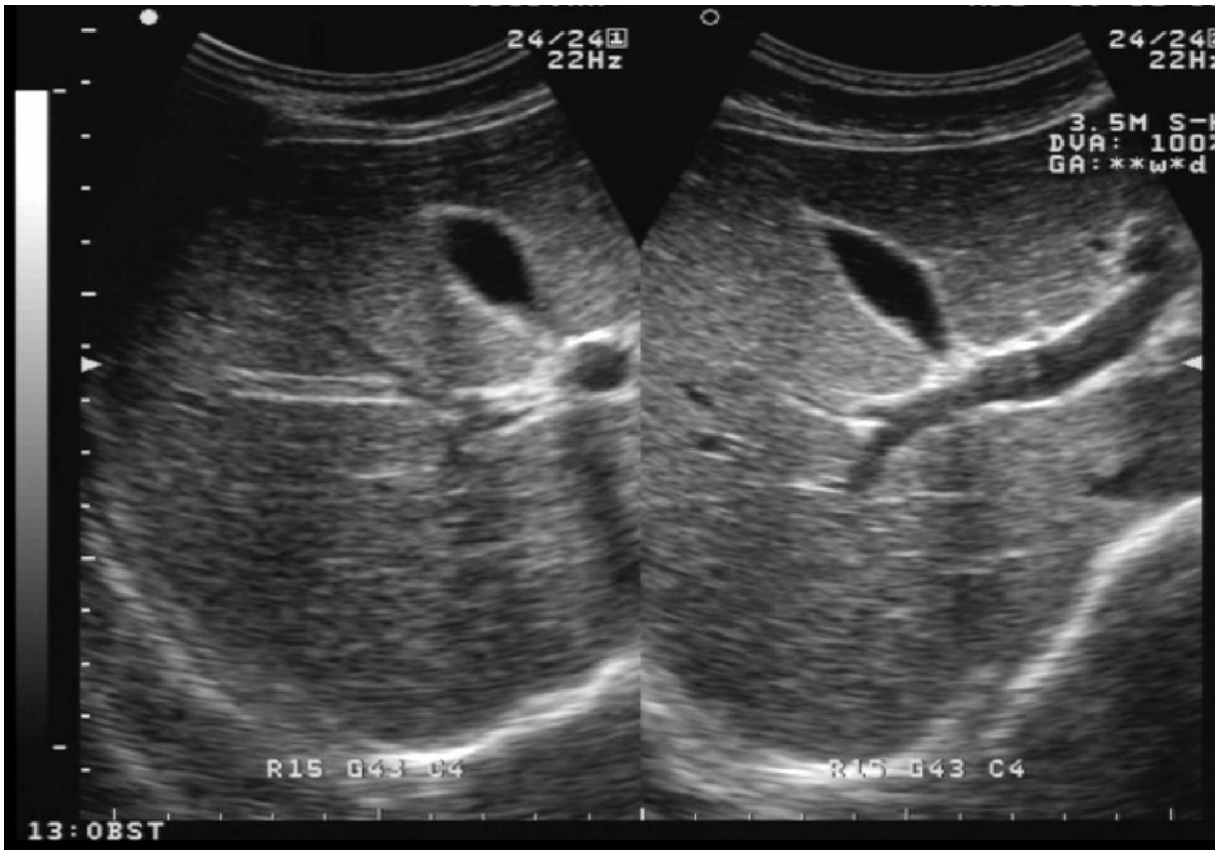

Figure 9. Ultrasonographic image showing highly echogenic pipestem fibrosis around the periportal veins, with echoes seen in two or three segments of the liver, in a man with opisthorchiasis.

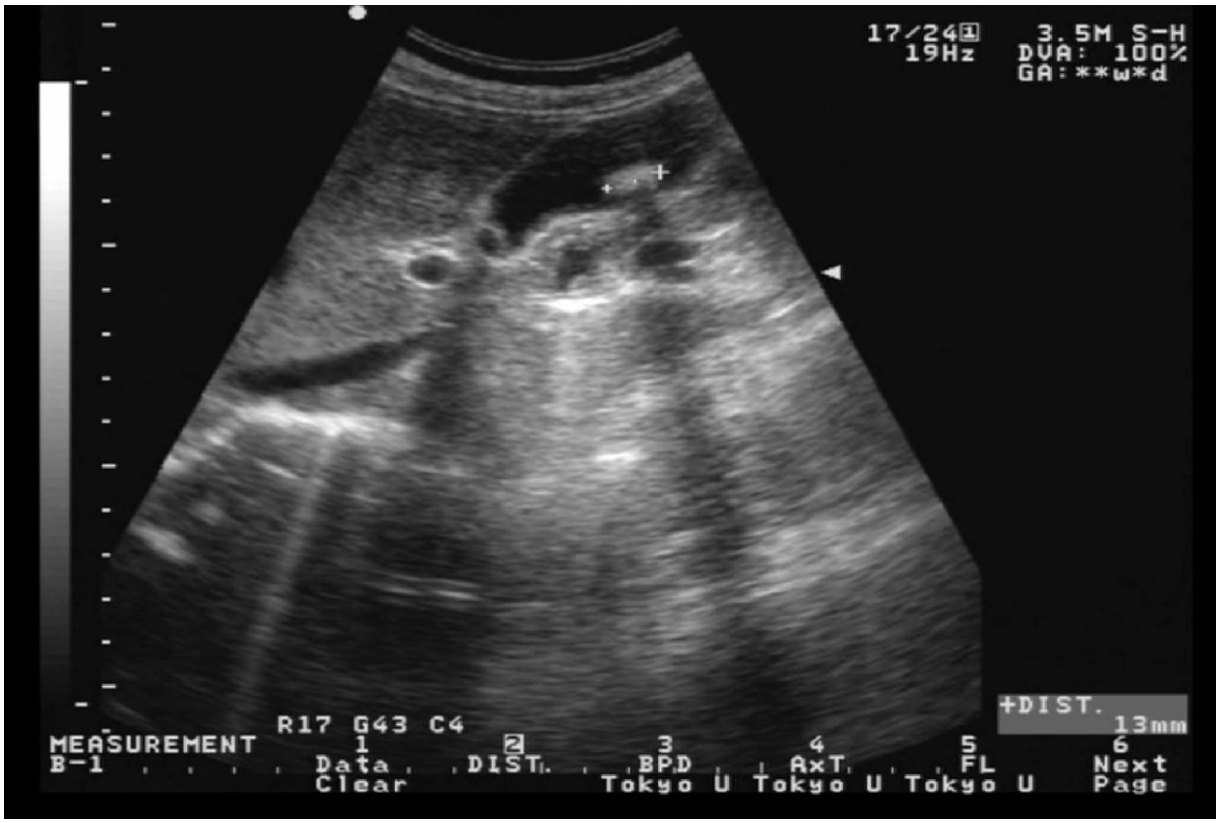

Figure 10. Ultrasonographic image showing echogenic posterior acoustic shadowing or biliary duct stone formation without bile duct dilation in a woman with opisthorchiasis.

Table 7. Clinical features of main food-borne trematodiasis.

Parasitosis	Tropism	Start	Symptoms and signs	Complications
Clonorchiasis and opisthorchiasis	Hepatobiliary tract	Insidious for several years: non-specific abdominal pain	Biliary colic, jaundice, cholestasis, cholelithiasis, recurrent pyogenic cholangitis, cholecystitis, hepatic abscess, rarely hepatitis	Pancreatitis, cirrhosis, portal hypertension, cholangiocarcinoma
Fascioliasis		Abrupt start: 1-4 weeks after infection high fever, weakness, weight loss, urticaria, right hypochondrial pain		Pancreatitis, cirrhosis, portal hypertension, rarely ectopic infection
Paragonimiasis	Pulmonary tract	Insidious: anorexia, moderate weight loss, rarely fever	Chronic cough, chest pain, dyspnoea, haemoptysis, rusty sputum	Bronchiectasis, pulmonary consolidation, cyst formation, pleural effusion, ectopic infection
Intestinal fluke infections	Intestinal tract	Insidious: unspecific gastrointestinal problems	Ulceration of intestinal mucosa, malabsorption	Malnutrition, anaemia, oedema or anasarca, rarely ectopic infection

5.3.2. Fascioliasis

Unlike other liver flukes, after ingestion and excystment in the duodenum *Fasciola* spp. migrate through the intestinal wall into the body cavity and then through the liver into the bile ducts.[11,15] Major pathological changes are associated with migration and the related destruction, focal bleeding, and inflammation in the host's body (acute phase). Some migrating flukes may die on their way, leaving cavities filled with necrotic debris, or deviate from their usual route to cause ectopic infections (Box 3). In the bile ducts (latent phase), the parasites may cause inflammation, resulting in thickening and expansion of the ducts and fibrosis. Imaging may depict these lesions as "tunnels and caves" in peripheral parts of the liver.[4]

Early acute manifestations are typical (Table 7).[8,11,15] Although some infected people are asymptomatic in the latent phase, others may experience repeated relapses of the acute manifestations.[8,11,15] When the irritation in the biliary system is severe enough, a permanent obstructive phase, which has additional symptoms, signs, and complications (Table 7), may develop.[3,4,8,9,11,15] Rarely, fascioliasis can be fatal.[15,w26]

Box 3: Ectopic food-borne trematode infections.

Pathological consequences and clinical manifestations: *Paragonimus* spp., and less often *Fasciola* spp. and intestinal flukes of the families heterophyidae and microphallidae, can cause ectopic infections. The reasons for incomplete migration are unclear. Migratory tracks and cavities filled with trapped dead parasites or eggs often cause tissue damage with inflammatory reactions and fibrosis. Clinical manifestations depend on the exact location, and such infections can even cause death. *Paragonimus* spp. have been reported in the central nervous system, eyes, skin, heart, abdominal organs, and reproductive organs; *Fasciola* spp. in the central nervous system, orbit, subcutaneous tissue, abdominal wall, heart, genitals, spleen, muscles, gastrointestinal tract, blood vessels, lungs, and pleural cavity; and heterophyidae and microphallidae in the central nervous system and heart.

Diagnosis: Suspect ectopic food-borne trematodiasis in a patient with a diagnosis of food-borne trematode infection and unexplained, often severe, manifestations (such as neurological disorders, abscesses) that could result from damage in ectopic locations mentioned above. To confirm the diagnosis, a combination of ultrasonography, radiography, endoscopy, computed tomography, positron emission tomography, magnetic resonance imaging, and biopsy is needed.

Management: Consultation with infectious disease specialists and other relevant specialists is recommended. Treatment with praziquantel or triclabendazole may help in the early phases of infection but should be used with care. Parasite death may lead to antigen release and increased risk of inflammation. Anti-inflammatory drugs (such as corticosteroids) may help to reduce oedema and inflammation during treatment. Parasites, eggs, and lesions may need to be surgically removed. Adjuvant therapy should be used as appropriate.

5.3.3. Paragonimiasis

In the classic natural course of pleuropulmonary paragonimiasis, swallowed metacercariae of *Paragonimus* spp. excyst in the duodenum, penetrate the intestinal wall, and migrate over several days to the pleural cavity and into the lungs where they mature. After several weeks, adults become encapsulated in fibrotic tissue, where they mate or reproduce parthenogenetically. Eggs pass via the bronchioles into the sputum or, if swallowed, the faeces, and then into the environment. Some of the eggs may be trapped in tissue and, together with aberrantly migrating flukes, provoke further irritation and ectopic infections (Box 3).[6,9,11,22] A recent cross sectional study from India found cavity and cyst formations, nodular lesions, fibrotic infiltrates, calcifications, bronchiectasis, pulmonary consolidations, pleural thickening and effusion, mediastinal lymphadenopathy, and patchy ground glass opacity as pleuropulmonary radiological features in paragonimiasis (Figure 11).[23]

Unless the patient is heavily infected, early stages of pleuropulmonary infection tend to be asymptomatic. Heavy pleuropulmonary infections may present with many different bronchitis-like, asthma-like, and tuberculosis-like symptoms and signs (Table 7). The similarity of the clinical manifestations often result in pleuropulmonary paragonimiasis being misdiagnosed as bronchitis, asthma, or (non-responsive) tuberculosis,[3,6,9,11,22] even though patients with paragonimiasis usually present in comparatively better general health.

5.3.4. Intestinal fluke infection

More than 70 species of intestinal flukes are implicated in human infection.[2,5] The morphology of these flukes is diverse, and their life cycles and geographical distributions not well studied. After ingestion of viable metacercariae, flukes excyst and adhere to the intestinal wall, where mechanical irritation and inflammation may lead to the manifestations described in Table 7.[3,5,9,11] Similar to other food-borne trematode infections, mild intestinal fluke infections are mainly asymptomatic, but heavy infections can be severe.[3,5,9,11,w27]

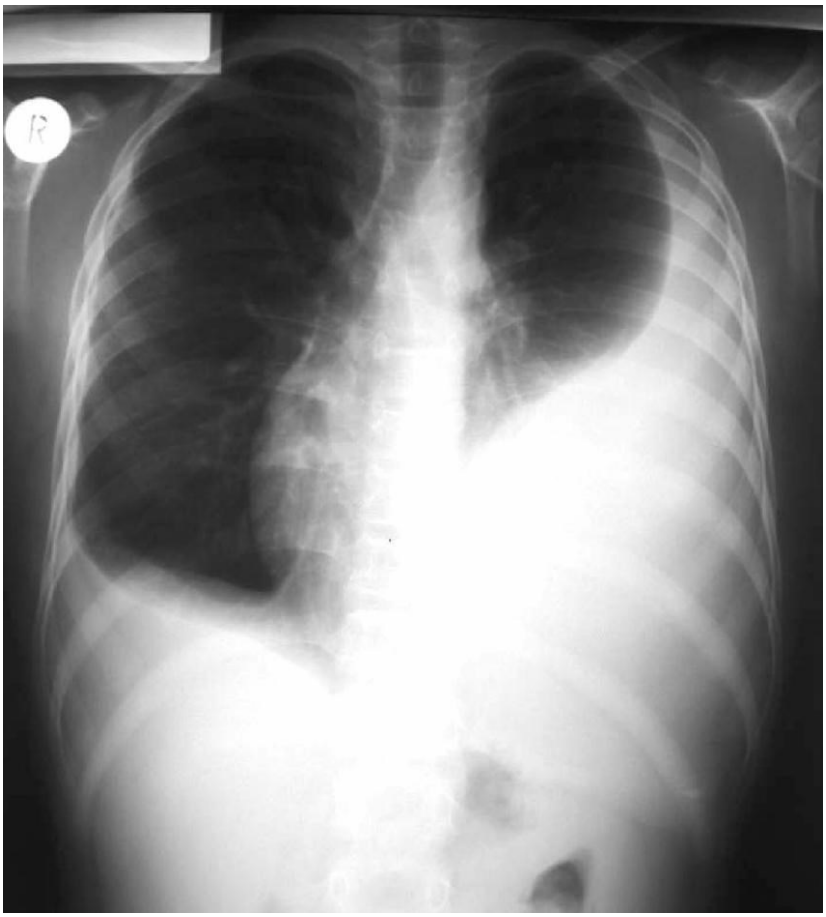

Figure 11. Chest radiograph of a 14 year old boy with paragonimiasis and a bilateral pleural effusion. He had chronic cough, chest pain (>12 months), and haemoptysis. Aspiration showed a thick chylous-like fluid containing 16% eosinophils and 20 typical trematode operculated eggs per mL. *Paragonimus* eggs were found in sputum and stool samples. He admitted that he often ate raw river crabs.[w52] Courtesy of the Institut de la Francophonie pour la Médecine Tropicale (IFMT), Lao People's Democratic Republic.

5.4. What are other complications of food-borne trematodiasis?

Recent reviews have summarised the association between infection with *C. sinensis* and *O. viverrini* and cholangiocarcinoma, as well as the mechanisms of carcinogenesis, diagnosis, and management (Box 2).[21,24,25,w8,w27-w33] On the basis of the epidemiological, experimental, and pathological evidence, these two trematodes have been classified as definite carcinogens (group 1) by the International Agency for Research on Cancer (IARC).[26,27] There is still insufficient evidence of the oncogenic potential of *O. felineus* and *Fasciola* spp. for them to be classified.[26,27,w28,w34]

Ectopic infections are severe and potentially fatal complications of food-borne trematodiasis (Box 3). As highlighted in other reviews, *Paragonimus* spp.,[6,9,11,22,w5,w11,w35-w39] and more rarely *Fasciola* spp. and intestinal flukes of the heterophyidae and microphallidae

families,[9,11,15,w26,w27] do not always enter their usual target organs in the host's body, but continue to migrate to ectopic locations.

5.5. How can food-borne trematodiasis be diagnosed?

Accurate diagnosis of food-borne trematodiasis remains a challenge. The three main diagnostic approaches are direct parasitological diagnosis, immunodiagnosis, and molecular diagnosis. Direct parasitological diagnosis is facilitated by the detection of eggs in faeces (all flukes), sputum (only lung flukes), and, more rarely, other biofluids such as bile or duodenal content. Egg detection in faecal samples is the most common approach, and methods include Kato-Katz thick smear, formalin-ethyl-acetate technique, Stoll's dilution egg count method, and sedimentation techniques. However, differential diagnosis is difficult because parasite eggs from different species resemble each other.[3-8,11] Furthermore, the small number of eggs discharged by some fluke species, crowding effects, obstructions in the patients' organs, heterogeneous distribution of eggs in the patients' faeces (or sputum in *Paragonimus* spp.), and light infections are additional challenges for an accurate diagnosis and require multiple sampling and testing. Occasionally, it is possible to demonstrate adult parasites—for example, when the flukes are excreted in the faeces, coughed up (lung flukes), or removed during surgery.[5,7-9,11] The website of the US Centers for Disease Control and Prevention features photographs of parasite eggs, which might help in the diagnosis of food-borne trematode infections.

Immunodiagnostic methods such as intradermal tests, indirect haemagglutination assays, indirect fluorescent antibody tests, and indirect enzyme linked immunosorbent assays (ELISAs) aim to detect specific antibodies.[3,6-8,11] Immunodiagnosis is especially useful during the prepatent phase and ectopic infections, or if direct parasitological diagnosis is ambiguous. However, false positive results after the infection has resolved, cross reactivity, high costs, and lack of availability at the point of care in remote rural areas are important problems that need to be tackled.[3,6,7]

Molecular diagnosis—the detection of trematode DNA in samples using the polymerase chain reaction—has a high sensitivity and specificity.[3,6-8,11] However, for the foreseeable future, molecular diagnosis is unlikely to be used at the point of care in endemic areas.[3,6]

Radiological methods such as ultrasound, computer tomography, and magnetic resonance imaging are complementary tools for an accurate diagnosis. Although these techniques might be available in well equipped laboratories in the developed world and undoubtedly help

characterise pathological changes caused by food-borne trematodiasis, they are currently out of reach in resource constrained areas.[3,6-9,11]

5.6. How can food-borne trematodiasis be treated?

Praziquantel and triclabendazole are the two drugs of choice; however, triclabendazole is currently registered for human use in only four countries. Various treatment regimens are suggested for the treatment of food-borne trematodiasis.[3,5-8,11,28,w40] For clonorchiasis and opisthorchiasis, the recommended treatment schedule is praziquantel 25 mg/kg three times a day for two consecutive days.[3,7,11,28] The same treatment regimen has been successfully used in paragonimiasis.[3,6,11,28] The first choice treatment against intestinal fluke infections is also praziquantel, and a single dose of 10-20 mg/kg is efficacious against all intestinal fluke species,[29] but higher dosages of three times 25 mg/kg in one day have also been proposed.[3,5,8,11,28] The drug of choice against fascioliasis is a single (10 mg/kg) or double dose (two times 10 mg/kg) of triclabendazole. [3,8,11,28] Triclabendazole (single dose of 10 mg/kg, or two doses of 10 mg/kg each within 12-24 hours) is also efficacious against paragonimiasis.[3] In general, all treatments are safe with no serious adverse events. Table 8 summarises the dosages of praziquantel, triclabendazole, and alternative drugs, including reported adverse events and contraindications. Figure 12 shows a diagnostic and treatment algorithm.

Table 8. Oral drugs and dosages for human food-borne trematodiasis.

Parasite	Drug	Dosage	Adverse events (AE)	Limitations to use and main contraindication(s)
Clonorchis sinensis	Praziquantel[a,c]	25 mg/kg 3 times a day for 2 days (40 mg/kg single dose in preventive chemotherapy)	Common AE include mild and transient insomnia, nausea, headache, dizziness, vomiting, and abdominal pain; less common AE include rash, hypotension, and sudden expulsion of worms aggravating obstruction	Restrained use in pregnant or breastfeeding women and children <4 years. Main contraindications are hypersensitivity and cysticercosis
	Albendazole[b,d]	10 mg/kg single dose for 7 days	Occasional AE include abdominal pain, reversible alopecia, and increased serum transaminases; rare AE include leucopenia, rash, and renal toxicity	Restrained use in pregnant women and children <1 year. Main contraindications are hypersensitivity and cirrhosis
Opisthorchis spp.	Praziquantel[a,c]	25 mg/kg 3 times a day for 2 days (40 mg/kg single dose in preventive chemotherapy)	Common AE include mild and transient insomnia, nausea, headache, dizziness, vomiting, and abdominal pain; less common AE include rash, hypotension, and sudden expulsion of worms aggravating obstruction	Restrained use in pregnant or breastfeeding women and children <4 years. Main contraindications are hypersensitivity and cysticercosis
Fasciola spp.	Triclabendazole[a,e]	10 mg/kg single dose (which may be repeated after 12-24 h in heavy infections)	Common AE include mild and transient abdominal and epigastric pain, sweating, and eosinophilia; less common AE include nausea, vomiting, headache, dizziness, cough, fever, urticaria, pruritus, and skin rash	Restrained use in pregnant or breastfeeding women, people with ectopic infections, and children <6 years. Main contraindication is hypersensitivity
	Bithionol[f]	30-50 mg/kg 10-15 doses on alternate days	Common AE include photosensitivity reactions, vomiting, diarrhoea, abdominal pain, and urticaria; rare AE include leucopenia and toxic hepatitis	Use with caution in people with ectopic infections and children <8 years

Table 8. Continued.

Parasite	Drug	Dosage	Adverse events (AE)	Limitations to use and main contraindication(s)
Paragonimus spp.	Praziquantel[a,c]	25 mg/kg 3 times a day for 2 days	Common AE include mild and transient insomnia, nausea, headache, dizziness, vomiting, and abdominal pain; less common AE include rash and hypotension	Restrained use in pregnant or breastfeeding women, people with ectopic infections, and children <4 years. Main contraindications are hypersensitivity and cysticercosis
	Bithionol[f]	30-50 mg/kg 10-15 doses on alternate days	Common AE include photosensitivity reactions, vomiting, diarrhoea, abdominal pain, and urticaria; rare AE include leucopenia and toxic hepatitis	Use with caution in people with ectopic infections and children <8 years
	Triclabendazole[a,e]	10 mg/kg single dose (which may be repeated after 12-24 h in heavy infections)	Common AE include mild and transient abdominal and epigastric pain, sweating, and eosinophilia; less common AE include nausea, vomiting, headache, dizziness, cough, fever, urticaria, pruritus, and skin rash	Restrained use in pregnant or breastfeeding women, people with ectopic infections, and children <6 years. Main contraindication is hypersensitivity
Intestinal flukes	Praziquantel[a,c]	10-20 mg/kg single dose or 25 mg/kg 3 times a day	Common AE include mild and transient insomnia, nausea, headache, dizziness, vomiting, abdominal pain, and diarrhoea; less common AE include rash, hypotension, and sudden expulsion of worms aggravating obstruction	Restrained use in pregnant or breast feeding women, people with ectopic infections, and children <4 years. Main contraindications are hypersensitivity and cysticercosis

The first choice treatment is the first one listed, but alternative drugs or dosages are also given.[11,28,29,w40-w42] [a]Take with liquids during a meal. [b]Take with liquids during a meal; a fatty meal increases bioavailability. [c]Manufacturers: Bayer (Biltricide), Shin Poong (Distocide). [d]Manufacturer: GlaxoSmithKline (Albenza). [e]Manufacturer: Novartis (Egaten). [f]Manufacturer: Tanabe Japan (Bitin).

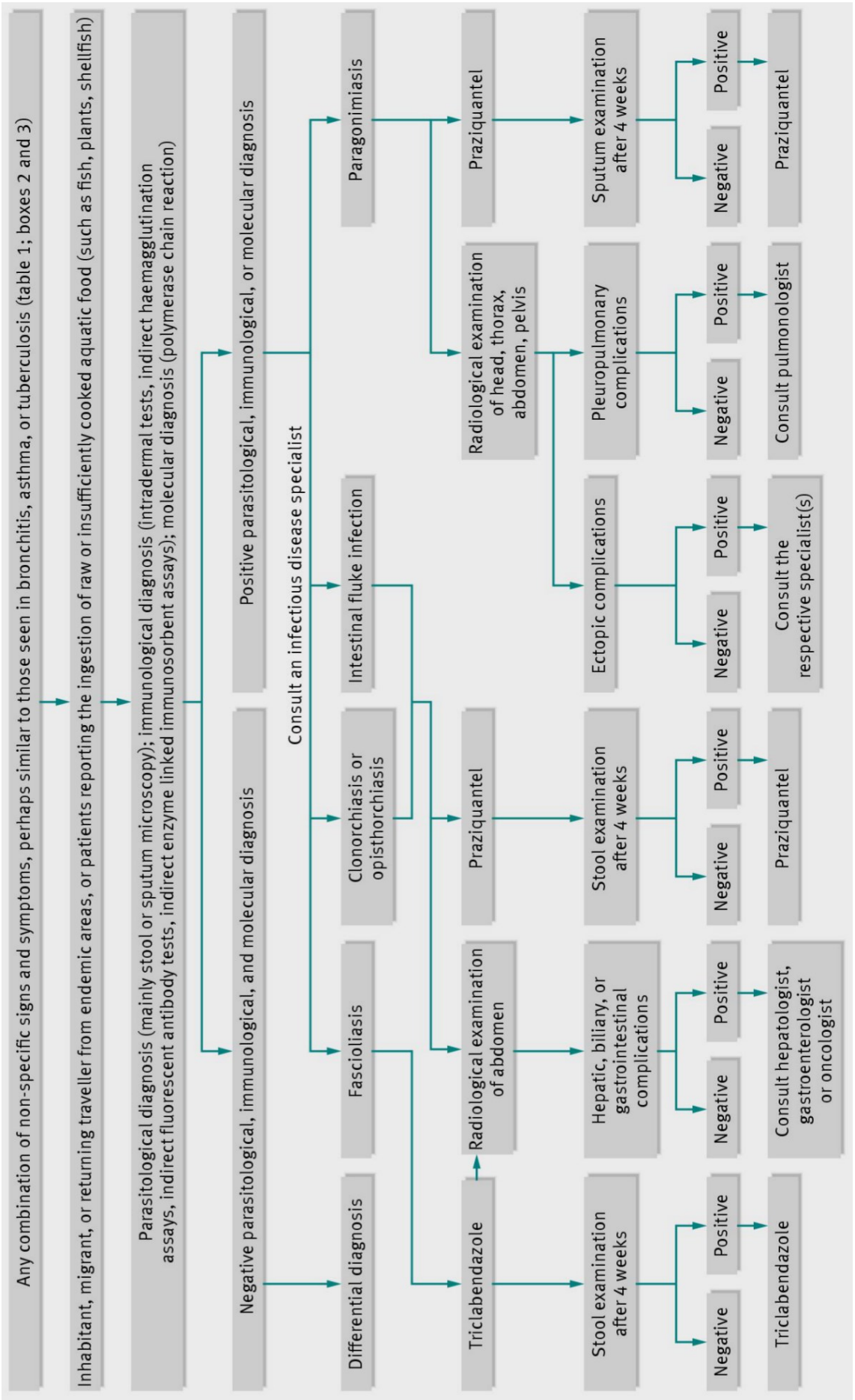

Figure 12. Algorithm for the diagnosis and treatment of food-borne trematodiasis.

5.7. Towards control and elimination: challenges and opportunities

New diagnostic techniques that have a high sensitivity and specificity and are simple and inexpensive are key to understanding the extent of the problem.[2] Improved point of care diagnostics could conceivably improve the management of cases and avoid severe sequelae.

The development of new drugs is a low priority for drug companies.[28] The treatment of food-borne trematodiasis currently relies on two drugs, and two small drug intervention studies reported unexpectedly low cure rates against clonorchiasis and fascioliasis.[30,31] A recent review recommended pursuing promising drug candidates (such as tribendimidine, the artemisinins, and synthetic trioxolanes) and combination treatments.[32] The development of vaccines for animals against infections with *Fasciola* spp. is at an advanced stage. Vaccination of animals and humans may become an important means of interrupting transmission.[33,w43]

Drugs are currently the main method of controlling the morbidity associated with food-borne trematodiasis, but integrated programmes are vital for sustainable disease control and eventual elimination.[11,15,19,w22,w27,w44,w45] Several follow-up studies highlighted the complexity of the epidemiological settings and showed high reinfection rates after drug based interventions.[w21,w46-w51] Hence, integrated control strategies should also include improved sanitation, food inspections, information, education, and communication campaigns (also for travellers) and, as far as feasible, control of intermediate, reservoir, and non-human definitive hosts. These additional interventions aim to change human behaviour and interrupt disease transmission.[3,6-9,11,21,w2,w30] However, considering deeply rooted eating habits in humans and the myriad non-human hosts these aims pose formidable challenges. Only a few endemic countries have embarked on national control programmes against food-borne trematodiasis. Integration with control programmes targeting other infectious diseases as well as collaborations beyond the health sector (such as with the agricultural, environmental, and educational sectors) may offer largely untapped opportunities for prevention and control.[9,34,w2]

A patient's perspective: opisthorchiasis in Lao People's Democratic Republic.

I am a 46 year old teacher and often go fishing in the Mekong River with friends. We eat the caught fish uncooked.

For more than a year I felt unwell—tired and without energy. I had many gastritis-like symptoms, such as abdominal pain, bowel rumbling, nausea, and bloating. I also had itchy rashes on my arms, stomach, and legs. I lost about 5 kg in weight but always felt hungry. After meals, particularly dinner, I often had stomach cramps and sometimes vomiting.

After repeated visits to different health services, I went to the hospital and had an abdominal ultrasound scan, in addition to blood and stool tests. The ultrasound results were normal and my blood was negative for hepatitis. However, liver fluke eggs were detected in my stool. I learnt that this parasite is acquired by consumption of raw fish and that after treatment I could be reinfected if I continue to eat undercooked fish. I received medicine called praziquantel. The rash on my arms, legs, and abdomen disappeared two weeks after treatment and I generally felt better. One month later my stool was free of parasite eggs. However, the abdominal discomfort disappeared only slowly. Three months after treatment, I occasionally have bowel rumbling, nausea, and abdominal bloating. My doctor assures me that the cure takes time and that it is most important not to eat raw fish.

Additional educational resources for patients and healthcare professionals.

US Centers for Disease Control and Prevention website – one of the few fully functional, up to date, open access sources of information. It contains a wealth of data on the most important food-borne trematode infections and is suitable for healthcare professionals and patients.

www.cdc.gov/parasites/clonorchis

www.dpd.cdc.gov/dpdx/html/clonorchiasis.htm

www.cdc.gov/parasites/opisthorchis

www.dpd.cdc.gov/dpdx/html/opisthorchiasis.htm

www.cdc.gov/parasites/fasciola

www.dpd.cdc.gov/dpdx/html/fascioliasis.htm

www.cdc.gov/parasites/paragonimus

www.dpd.cdc.gov/dpdx/html/paragonimiasis.htm

www.cdc.gov/parasites/fasciolopsis

www.dpd.cdc.gov/dpdx/html/fasciolopsiasis.htm

www.dpd.cdc.gov/dpdx/html/echinostomiasis.htm

www.dpd.cdc.gov/dpdx/html/heterophyiasis.htm

www.dpd.cdc.gov/dpdx/html/metagonimiasis.htm

Areas for future research.

More precise data on the extent of the human and veterinary disease burden of food-borne trematode infections (geographical distribution, prevalence, infection intensity, coinfection, subtle morbidity, and societal impact) are needed to increase awareness (in patients and clinicians) and raise political commitment to foster control and elimination efforts

Additional studies should verify the taxonomy of food-borne trematodes and associated intermediate, reservoir, and definitive hosts

New diagnostic methods with a high sensitivity and specificity that are inexpensive and can be used at point of contact are needed

New trematocidal drugs and alternative treatment regimens (for example, multiple dosing, combination treatment) that are safe and efficacious need to be developed

Molecular research on the antigenic structure and immunology of food-borne trematodes and research into the immune mechanisms of infected humans and animals may be useful for vaccine development

A better knowledge of liver fluke induced carcinogenesis may improve the diagnosis, treatment, and prevention of cholangiocarcinoma and provide fundamental insights into carcinogenesis in general

Mechanisms of ectopic food-borne trematode infections should be further explored to improve diagnosis, treatment, and prevention of severe complications

Improved knowledge on physical and chemical parameters to inhibit infectivity of metacercariae could help to advance safe food processing methods and guidelines

The cost effectiveness of integrated control programmes for food-borne trematodes—which include different stakeholders, a variety of interventions (such as chemotherapy, improved sanitation, food inspections, information, education and communication campaigns, and control of non-human parasite life cycles), and that take advantage of synergy between different sectors (public health, livestock production, food industry, water and sanitation, socio-economic development, education)—should be determined

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(All references in the text beginning with ‘w’ are provided in a web reference list and shown in Appendix 13.1.)

6. Global burden of human food-borne trematodiasis: a systematic review and meta-analysis

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6.1. Summary

Background: Food-borne trematodiases are a group of neglected tropical diseases caused by liver, lung, and intestinal parasitic fluke infections. As part of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD 2010 study) and a WHO initiative, we assessed the global burden of human food-borne trematodiasis, as expressed in disability-adjusted life years (DALYs) for the year 2005.

Methods: We systematically searched electronic databases for reports about human food-borne trematodiasis without language restriction, between Jan 1, 1980, and Dec 31, 2008. We used a broad search strategy with a combination of search terms and parasite and disease names. The initial search results were then screened on the basis of title, abstract, and, finally, full text. Relevant quantitative and qualitative data on human prevalence, morbidity, and mortality of food-borne trematodiasis were extracted. On the basis of available information on pathological and clinical appearance, we developed simplified disease models and did meta-analyses on the proportions and odds ratios of specified sequelae and estimated the global burden of human food-borne trematodiasis.

Findings: We screened 33,921 articles and identified 181 eligible studies containing quantitative information for inclusion in the meta-analyses. About 56.2 million people were infected with food-borne trematodes in 2005, 7.9 million had severe sequelae, and 7,158 died, most from cholangiocarcinoma and cerebral infection. Taken together, we estimate that the global burden of food-borne trematodiasis was 665,352 DALYs (lower estimate 479,496 DALYs; upper estimate 859,051 DALYs). Furthermore, knowledge gaps in crucial epidemiological disease parameters and methodological features for estimating the global burden of parasitic diseases that are characterised by highly focal spatial occurrence and scarce and patchy information were highlighted.

Interpretation: Despite making conservative estimates, we found that food-borne trematodiases are an important cluster of neglected diseases.

Keywords: Global burden of diseases, food-borne trematodiasis, disability-adjusted life years (DALYs), review, meta-analysis.

6.2. Introduction

Our analysis of the global burden of human food-borne trematodiasis is part of the Global Burden of Diseases, Injuries, and Risk Factors Study (the GBD 2010 study)[1] and an initiative by WHO to estimate the global burden of food-borne diseases, facilitated by WHO's Food-borne Disease Burden Epidemiology Reference Group (FERG).[2] Food-borne trematodiases are a cluster of infections with trematodes transmitted by consumption of undercooked, mainly aquatic, products. Species-specific life cycles have been presented elsewhere.[3] Although the first documented cases of human food-borne trematodiasis date back several thousand years,[3,4] uncertainty remains about taxonomy, with new species being identified and described.[5,6] Over 80 different species of food-borne trematode have been reported from human infections (Appendix 13.2.1.).[5-8]

Food-borne trematodes are classified as liver, intestinal, or lung flukes, on the basis of their typical location in the host. From a public health point of view, the most important species are *Clonorchis sinensis*, *Opisthorchis felineus*, *Opisthorchis viverrini*, *Fasciola gigantica*, and *Fasciola hepatica* among the liver flukes, *Echinostoma* spp., *Fasciolopsis buski*, *Heterophyes* spp., and *Metagonimus* spp. among the intestinal flukes, and *Paragonimus* spp. among the lung flukes.[5-8] Other species rarely infect human beings, and are less relevant to public health.

Direct parasitological techniques via detection of eggs in the hosts' faeces, sputum, and more rarely other biofluids (e.g., bile or duodenal content) are widely used for diagnosis. However, accurate detection and species-specific distinction of eggs is a challenge.[3,5-10] Immunodiagnostic techniques and molecular methods are comparatively resource and skill intensive alternatives and therefore unlikely to become methods for routine diagnosis in endemic settings in the foreseeable future.[3,6-8,10]

Chemotherapy is the mainstay for treatment and morbidity control of food-borne trematodiasis; drugs of choice are praziquantel (against clonorchiasis, opisthorchiasis, intestinal fluke infections, and paragonimiasis)[3,5-8,10,11] and triclabendazole (against fascioliasis).[3,7,10,11] Integrated control strategies, including preventive and curative measures such as improved access to adequate sanitation, information, communication, and education campaigns, food inspections, and, as much as possible, control of intermediate and final-reservoir hosts are essential.[3,6,7,9,10,12,13] Unfortunately, awareness of food-borne trematodiasis as a public health problem is limited, and hence only a few endemic countries (e.g., Japan and

South Korea) have successfully initiated or maintain fully fledged national control programmes.[9,13,14]

Because of the diversity of causative pathogens, diagnostic challenges, and idiosyncrasies in the natural histories of diseases, food-borne trematode infections are among the most neglected of the so-called neglected tropical diseases.[3,15,16] As with most other neglected tropical diseases, these trematode infections are intimately connected with and exacerbate conditions of poverty.[3,15,17] However, because consequences are not overt and morbidity often subtle, the social, economic, and public health effects of food-borne trematodiasis are underestimated, which might also explain previous lack of estimates of global burden.[3,15-18]

Our study had two aims: first, to estimate the global burden of human food-borne trematodiasis in terms of disability-adjusted life years (DALYs) by following the guidelines and concepts of the GBD 2010 study;[1] and second, to identify knowledge gaps in the respective epidemiological disease parameters. Furthermore, our method is presented and discussed in detail, because it could be useful for estimating the global burden of other parasitic diseases that are characterised by highly focal spatial occurrence and scarce, scattered, and patchy information.

6.3. Methods

6.3.1. Search strategy and selection criteria

We did a broad-based computer-aided systematic review to identify all relevant information about the global burden of food-borne trematodiasis. We searched PubMed, WHOLIS, FAOBIB, Embase, CAB Abstracts, Literatura Latino Americana e do Caribe em Ciências de Saùde (LILACS), ISI Web of Science, BIOSIS preview, Science Direct, African Journals OnLine (AJOL), and the System for Information on Grey Literature in Europe (SIGLE). A broad-based search strategy was used, applying, whenever available, the respective thesauruses of the databases, and a corresponding combination of search terms including specific parasite and disease names. No language restrictions were set. On the basis of GBD 2010 study guidelines,[1] all references published between Jan 1, 1980 and Dec 31, 2008 were reviewed. Further details on the databases and search terms that were checked, initial inclusion and exclusion terms, and, wherever applicable, the respective thesauruses, Boolean operators, and wildcards used are summarised in Appendix 13.2.1. and Appendix 13.2.2. The bibliographies of all finally included documents were hand-searched for additional references.

Further more, we did a targeted search for data that were classed as still missing on the basis of information obtained. Articles reporting on time-independent biomedical facts before 1980 and after 2008 were also included in a final step. The search of published works and data abstraction was done by TF. In case of ambiguity the other authors were consulted.

6.3.2. Simplified disease models

For the quantitative analyses, we divided food-borne trematodiasis into five disease categories: (1) clonorchiasis, (2) opisthorchiasis, (3) fascioliasis, (4) intestinal fluke infections, and (5) paragonimiasis. On the basis of identified qualitative information about pathological and clinical symptoms, and the availability of quantitative data, three different simplified disease models were constructed. These models permitted the quantification of global burden of all five food-borne trematodiasis categories, as expressed in DALYs (Figure 13, Box 4). In subsequent burden calculations, we gave highest priority to population-based quantitative data to avoid strong selection bias.

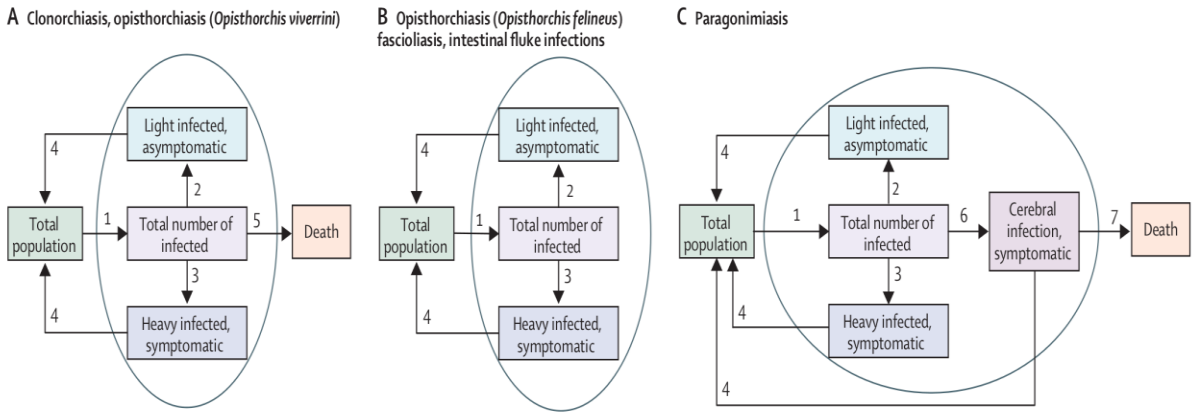

Figure 13. Simplified disease models used to estimate the global burden of food-borne trematodiasis. 1 = prevalence rate. 2 = proportion of light infections among all infections. 3 = proportion of heavy infections among all infections. 4 = remission rate. 5 = mortality rate due to liver-fluke-induced cholangiocarcinoma. 6 = proportion of cerebral infections among all *Paragonimus* spp. infections. 7 = mortality due to cerebral paragonimiasis.

Because of the focal occurrence of food-borne trematodiasis and resulting high variation in prevalences on a small spatial scale,[9,13] we only further assessed the most recent national prevalence estimates identified in the systematic review with priority given to estimates based on molecular diagnosis, then those based on direct parasitological diagnosis, immunodiagnosis, and, finally, expert opinion. Identified national prevalence rates were

multiplied by the official GBD 2010 study population estimates to project the total national numbers of infected people in 2005 (Figure 13).

Box 4. Pathological and clinical appearances of food-borne trematodiasis in humans.

Background: Human food-borne trematodiasis is species-specific and governed by the number of worms in the body (i.e., infection intensity), the duration of infection, and host susceptibility.[3,6-10] Pathological changes include inflammatory lesions, tissue damage, and damage of the target organs caused either directly through mechanical and chemical irritation by the parasites or indirectly through the hosts' immune response.[10]

Clonorchis sinensis and Opisthorchis viverrini: *C. sinensis* and *O. viverrini* can induce cholelithiasis, cholestasis, cholangitis, cholecystitis, biliary and liver abscess and cirrhosis, pancreatitis, hepatitis, and, as a most severe consequence, the bile-duct cancer cholangiocarcinoma (Figure 13).[3,8-10,19] Clinical manifestations range from asymptomatic, mostly light infections, to mild symptoms such as fever, fatigue, anorexia, and gastrointestinal complaints in moderate infections, to severe diarrhoea, sometimes in alternation with constipation, nausea, colicky pain, dyspepsia, malnutrition, and anaemia in heavy infections.[3,8-10,19] Even though the exact mechanism of cholangiocarcinogenesis is not yet fully understood, irritation caused by the parasites plays a crucial part.[12,19-21] The International Agency for Research on Cancer has classified *O. viverrini* as a definite carcinogen since 1994 and *C. sinensis* since 2009.[22,23] Cholangiocarcinoma is the most common cause of death attributable to food-borne trematodiasis. Timely diagnosis of this cancer is rare, because symptoms are mostly non-specific.[12,24] Hence, patients who finally seek care usually present with advanced, inoperable disease with very poor prognoses on diagnosis. Resection or transplantation are the only curative intervention, but often only palliative treatment remains and most patients die within a year after diagnosis.[12,24]

Opisthorchis felineus, Fasciola spp., and intestinal flukes: Patients with the liver flukes *O. felineus* and *Fasciola* spp. can present with the same pathological changes and clinical manifestations as *C. sinensis* and *O. viverrini* (Figure 13).[3,7-10] However, evidence for the carcinogenic potential of *O. felineus* and *Fasciola* spp. is not available.[22,23,25] Intestinal flukes can also cause intestinal obstruction and ulceration.[5,10] Rarely, the liver flukes *Fasciola* spp. and some of the intestinal flukes can substantially deviate from their usual migratory route in human hosts. These flukes have occurred in ectopic locations such as the skin, eyes, abdominal organs, heart, or CNS.[5,7,9,10,26,27] In very rare cases, infections with *Fasciola* spp., *Fasciolopsis buski,* heterophyidae, or microphallidae can be fatal,[5,9,10,26,28,29] but information on ectopic or fatal infections is very scarce.

Paragonimus spp.: Patients with lung-fluke infection can present with haemorrhagic pneumonia, pneumothorax, pleuropulmonary cysts, abscesses, and calcifications (Figure 13).[6,9,10,30] Heavy pleuropulmonary paragonimiasis is often characterised by tuberculosis-like, bronchitis-like, and asthma-like symptoms, such as chronic cough with bloody sputum, chest pain, and dyspnoea.[3,6,9,10] Among the food-borne trematodes, *Paragonimus* spp. is most commonly associated with ectopic infections. The most common extrapulmonary location of *Paragonimus* spp. is the brain,[6,30] and in rare cases the skin, eyes, abdominal organs, genitalia, or other parts of the CNS.[3,6,9,10] Patients with cerebral infection can present with headache, mental confusion, behavioural change, meningismus, convulsions, hemiplegia, visual impairment, and cerebral haemorrhage. Cerebral infection is the most common cause of death due to paragonimiasis[3,6,9,10,30] with most deaths occurring at the beginning of cerebral involvement.[6,31]

To distinguish male and female cases, all sex-specific population-based data from cross-sectional surveys were aggregated and prevalence sex ratios for the five food-borne trematodiasis categories were established. Similarly, these data from cross-sectional surveys were used to create sex-specific age prevalence profiles for each food-borne trematodiasis category, except fascioliasis. Because of insufficient sex-specific and age-specific data on fascioliasis, the respective age prevalence profile was not further differentiated between males and females. To harmonise the reported age categories from the identified studies with those of the GBD 2010 study,[1] we assumed an equal distribution of the number of people examined and infected over the different ages included in each reported age category. To differentiate between asymptomatic and symptomatic cases, we had to rely on infection intensities (Figure 13). The number of parasite eggs per g of faeces or, for paragonimiasis, the number of parasite eggs per 5 mL of sputum are the most commonly used proxies for infection intensity.[3,6-10,19,26,32-41] On the basis of available information, disease-specific thresholds for heavy infections were set at 10,000 eggs per g of faeces for clonorchiasis and opisthorchiasis, 1,000 eggs per g of faeces for fascioliasis and intestinal fluke infections, and 100 eggs per 5 mL of sputum for paragonimiasis. All age-independent and sex-independent population-based cross-sectional survey data on the proportion of heavily infected individuals among all infected individuals were used to model the proportion of light, asymptomatic infections and heavy, symptomatic infections. Furthermore, all age-independent and sex-independent population-based data on the proportion of cerebral involvement in all patients with *Paragonimus* spp. infection were assessed for the extrapolation of the number of cerebral paragonimiasis cases. Data on remission from the different stages of food-borne trematodiasis are scant and as initial model input, we assumed zero remission.

Because of few quantitative data, mortality rate estimates relied partly on hospital-based case-control studies and case series and were modelled irrespective of infection intensity. Mortality from *C. sinensis* and *O. viverrini* infections were modelled as attributable cases of cholangiocarcinoma (Figure 13). All information on odds ratios between *C. sinensis* and *O. viverrini* infection and cholangiocarcinoma from age-independent and sex-independent case-control studies and large (>100) autopsy series were incorporated. The resulting odds ratios were then combined with the cholangiocarcinoma incidence rate of a population, which is highly affected by liver flukes (north-east Thailand),[42] to calculate the incidence rate of this carcinoma, which is attributable to liver-fluke infections. Because of poor prognosis of patients with cholangiocarcinoma, incidence rates of this disease attributable to liver-fluke infections were set equal to mortality rates.

Mortality from *Paragonimus* spp. infection was modeled on the basis of information about the proportion of deaths among all patients with paragonimiasis and cerebral involvement in all identified case series (Figure 13). Since most fatal cases occur at the beginning of cerebral infection,[6,31] the proportion of deaths was multiplied by the incidence rate of cerebral paragonimiasis to obtain the attributable number of deaths.

6.3.3. Statistical analysis

Quantitative information about infection intensity, odds ratios for cholangiocarcinoma, cerebral involvement, and mortality attributable to food-borne trematodiasis was entered into StatsDirect (version 2.7.2) for meta-analysis. Random-effect models were used to account, at least partly, for data heterogeneity (Cochran's Q statistic with $p < 0{\cdot}001$ for all datasets).

To transform all the reviewed information into DALY estimates, we used DisMod 3. This software replaced earlier DisMod versions and was especially developed for the GBD 2010 study. On the basis of Bayesian models and a minimum of three of five epidemiological key indicators (i.e., prevalence, incidence, remission, mortality, and duration), the software computed an internally consistent and complete set of all five epidemiological key indicators.[1] In an iterative process, key indicators for each sequela attributable to food-borne trematodiasis were calculated and assessed with regard to initial inputs and expert opinion. Bayesian model priors were adjusted in DisMod 3 on the basis of expert opinion to force model outputs to be internally and logically consistent and plausible. Once a set of five epidemiological key indicators was accepted, it was combined with the most recent version of already established disability weights of similar sequelae (Table 9)[43] to calculate DALYs.

If applicable, 95% CIs and credible intervals were added for analysis of uncertainty in DisMod 3 input and output. However, no 95% CIs were calculated for initial country-wide prevalence estimates because they were mainly based on expert opinion. Furthermore, no credible intervals could be established for the resulting total numbers of infected people because of DisMod 3 model specifications. Moreover, no 95% CIs were given for sex and age profiles because they were only used for assigning the cases to the different sex-specific and age-specific groups.

Table 9. Disability weights used for the calculation of the disability-adjusted life years due to food-borne trematodiasis.

Sequela	Most similar sequela from GBD 2004	Weight
Heavy clonorchiasis	Schistosomiasis: advanced hepatic disease	0.104
Heavy opisthorchiasis	Schistosomiasis: advanced hepatic disease	0.104
Heavy fascioliasis	Schistosomiasis: advanced hepatic disease	0.104
Heavy intestinal fluke infection	Intestinal nematode infection: massive dysentery syndrome	0.116
Heavy paragonimiasis	Lower respiratory infection: chronic sequelae	0.099
Cerebral paragonimiasis	Meningitis: seizure disorder	0.100

Most recent version of already established disability weights of most similar sequelae were selected from the WHO Global Burden of Disease (GBD) 2004 update.[43] By definition, disability weights range on a scale from 0 (perfect health) to 1 (death).

6.3.4. Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

6.4. Results

Our systematic review identified 33,921 studies; 181 were included in the quantitative analyses (Figure 14, Appendix 13.2.3. and Appendix 13.2.4.). The highest national prevalence rates of food-borne trematodiasis occurred with regard to *O. viverrini* in Laos and Thailand (Table 10). More men than women were infected with *C sinesis*, *Opisthorchis* spp., all intestinal flukes, and *Paragonimus* spp., whereas slightly more women than men were infected with *Fasciola* spp. (Table 11). Most pronounced sex-specific and age-specific prevalence profiles were for *C. sinensis* with prevalences in 45-54 year-old men more than nine-times higher than prevalences in 1-4 year-old boys (Figure 15).

Meta-analysis of proportions of heavy and therefore symptomatic infections among all infections resulted in estimates of 26.0% for paragonimiasis, 15.4% for intestinal fluke infections, 14.0% for fascioliasis, 8.2% for clonorchiasis, and 4.9% for opisthorchiasis (Appendix 13.2.5.). We identified only one high-quality, population-based study with information on the proportion of cerebral involvement among all cases of paragonimiasis.[50] Unfortunately, this study from South Korea gave no information on infection intensities, but showed that 0.8% of all patients with paragonimiasis could have cerebral infection.

With *C. sinensis* infection the odds ratio for cholangiocarcinoma was 6.1; with *O. viverrini* infection the odds ratio was 4.4. These ratios were established in meta-analyses and needed as proxies for estimating mortality (Appendix 13.2.6.). Meta-analysis of proportions of deaths among all patients with paragonimiasis and cerebral involvement resulted in a proportion of 10.0% (Appendix 13.2.7.).

Outputs from the DisMod 3 models for relevant sequelae are shown in Appendix 13.2.8. Remission rates deviated from the initial model input of zero remission. Overall, our estimates showed that 56.2 million people might be infected with food-borne trematodes (Table 12). About 7.9 million people (7.2-8.8) were modelled as having heavy or cerebral infections. The estimated number of deaths for 2005 was 7,158 (5,795-8,952). These figures resulted in 351,026 years lived with disability (224,847-466,042) and 314,326 years of life lost (254,649-393,009). Taken together, we estimate that, in 2005, the global burden due to food-borne trematodiasis was 665,352 DALYs (479,496-859,051). All lower and upper estimates based on 95% CIs and credible intervals are shown in Appendix 13.2.9.

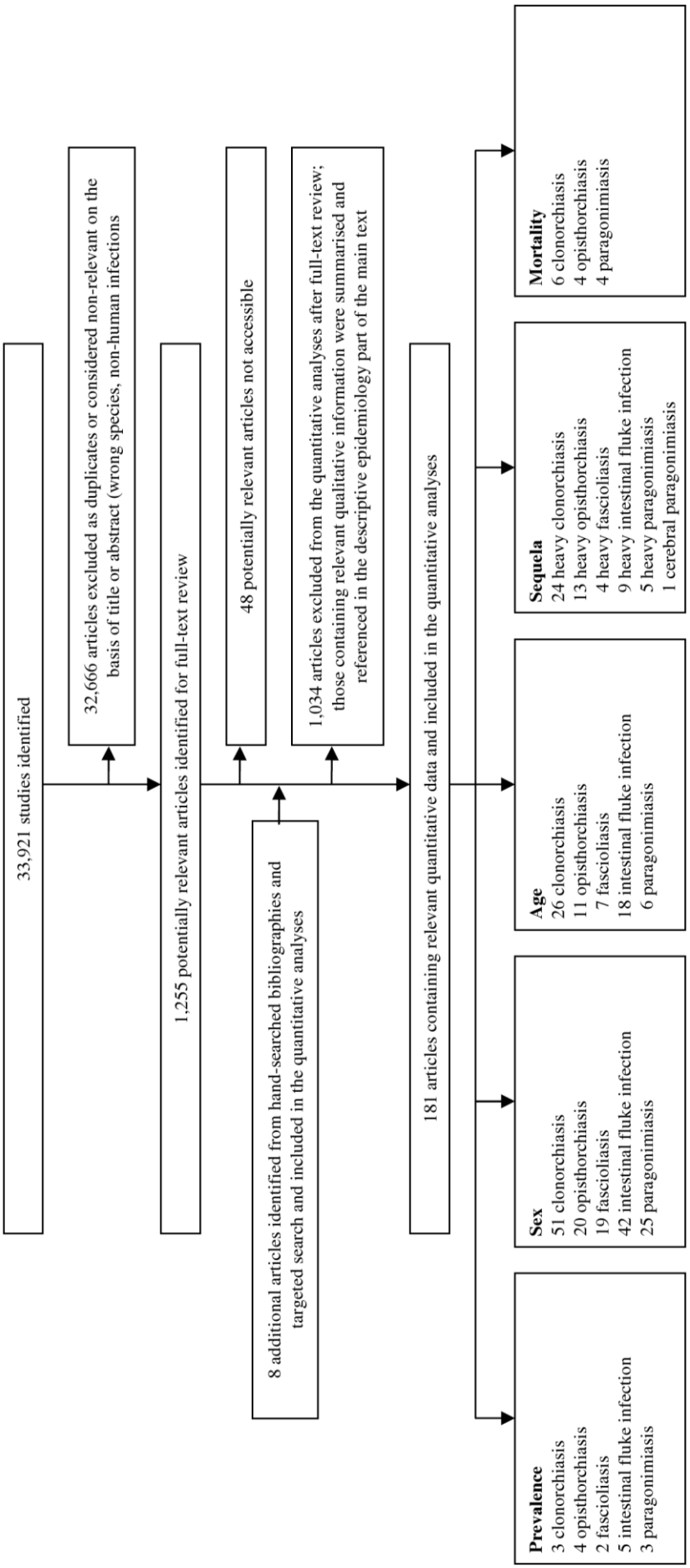

Figure 14. Study selection. References containing solely qualitative information on food-borne trematodiasis are summarised and referenced in the main text. References containing quantitative datasets for the estimation of the global burden of food-borne trematodiasis are referenced in Appendix 13.2.3. and Appendix 13.2.4.

Table 10. Country-specific and parasite-specific prevalence rates used for the extrapolation of the total number of human food-borne trematodiasis cases.

Parasite	Reference	Country	Study type	Year of study	Most recent prevalence used for projections (%)	Total number of people examined	Diagnostic technique
Liver flukes							
Clonorchis sinensis	[44]	China	National Survey	2001-04	0.951	574,458	Coprology
	[9]	Hong Kong	Expert opinion	1995	5.633	NA	NA
	[9]	Macau	Expert opinion	1995	4.225	NA	NA
	[45]	South Korea	National Survey	2004	2.417	20,264	Coprology
	[9]	Russia	Expert opinion	1995	0.002	NA	NA
	[9]	Vietnam	Expert opinion	1995	1.467	NA	NA
Opisthorchis viverrini	[13]	Laos	Expert opinion	2004	37.020	NA	NA
	[46]	Thailand	National Survey	2001	9.415	1,062,725	Coprology
Opisthorchis felineus	[9]	Kazakhstan	Expert opinion	1995	0.293	NA	NA
	[47]	Russia	Expert opinion	2001	0.030	NA	NA
	[9]	Ukraine	Expert opinion	1995	0.601	NA	NA
Fasciola spp.	[9]	Bolivia	Expert opinion	1995	4.729	NA	NA
	[48]	China	National Survey	1988-92	0.011	1,477,742	Coprology
	[9]	Ecuador	Expert opinion	1995	0.185	NA	NA
	[9]	Egypt	Expert opinion	1995	1.520	NA	NA
	[9]	Iran	Expert opinion	1995	0.018	NA	NA
	[9]	Peru	Expert opinion	1995	3.373	NA	NA
	[9]	Portugal	Expert opinion	1995	0.025	NA	NA
	[9]	Spain	Expert opinion	1995	0.003	NA	NA

Table 10. Continued.

Parasite	Reference	Country	Study type	Year of study	Most recent prevalence used for projections (%)	Total number of people examined	Diagnostic technique
Intestinal flukes							
Echinostoma spp.	13	South Korea	Expert opinion	2004	0.121	NA	NA
	49	Philippines	National Survey	1967-83	3.000	33,857	Coprology
	48	China	National Survey	1988-92	0.015	1,477,742	Coprology
Fasciolopsis buski	48	China	National Survey	1988-92	0.169	1,477,742	Coprology
	13	Thailand	Expert opinion	2004	0.016	NA	NA
Gymnophallidae	13	South Korea	Expert opinion	2004	0.085	NA	NA
Metagonimus spp.	45	South Korea	National Survey	2004	0.470	20,264	Coprology
	13	Japan	Expert opinion	2004	0.118	NA	NA
	9	Russia	Expert opinion	1995	0.008	NA	NA
Other Heterophyidae	9	Egypt	Expert opinion	1995	0.019	NA	NA
	13	South Korea	Expert opinion	2004	0.252	NA	NA
	49	Philippines	National Survey	1967-83	1.000	14,265	Coprology
	48	China	National Survey	1988-92	0.021	1,477,742	Coprology
Nanophyetus spp.	9	Russia	Expert opinion	1995	0.012	NA	NA
Neodiplostomidae	13	South Korea	Expert opinion	2004	0.002	NA	NA
Plagiorchiidae	13	South Korea	Expert opinion	2004	0.001	NA	NA
Lung flukes							
Paragonimus spp.	44	China	National Survey	2001-04	1.700	68,209	Serology
	9	Ecuador	Expert opinion	1995	4.568	NA	NA
	9	Laos	Expert opinion	1995	3.590	NA	NA
	9	Peru	Expert opinion	1995	0.123	NA	NA
	45	South Korea	National Survey	2004	0.002	20264	Coprology

NA = not applicable.

Table 11. Parasite-specific and sex-specific prevalence rates of food-borne trematodiasis and derived standardised prevalence sex ratios.

Parasite	Male			Female			Sex ratio (male:female)
	Total examined	Total infected	Prevalence (%)	Total examined	Total infected	Prevalence (%)	
Clonorchis sinensis	977,113	42,274	4.326	965,957	22,726	2.353	1.839
Opisthorchis spp.	19,864	7,398	37.243	26,624	8,249	30.983	1.202
Fasciola spp.	758,660	1,535	0.202	768,630	1,589	0.207	0.979
All intestinal flukes	2,273,007	5,866	0.258	2,306,863	4,887	0.212	1.218
Paragonimus spp.	109,879	10,344	9.414	157,096	11,670	7.429	1.267

All sex-specific population based cross-sectional survey data identified in the systematic review were aggregated to calculate male-to-female prevalence ratios. Bibliographic details on the references of the quantitative datasets included are in Appendix 13.2.3. und Appendix 13.2.4.

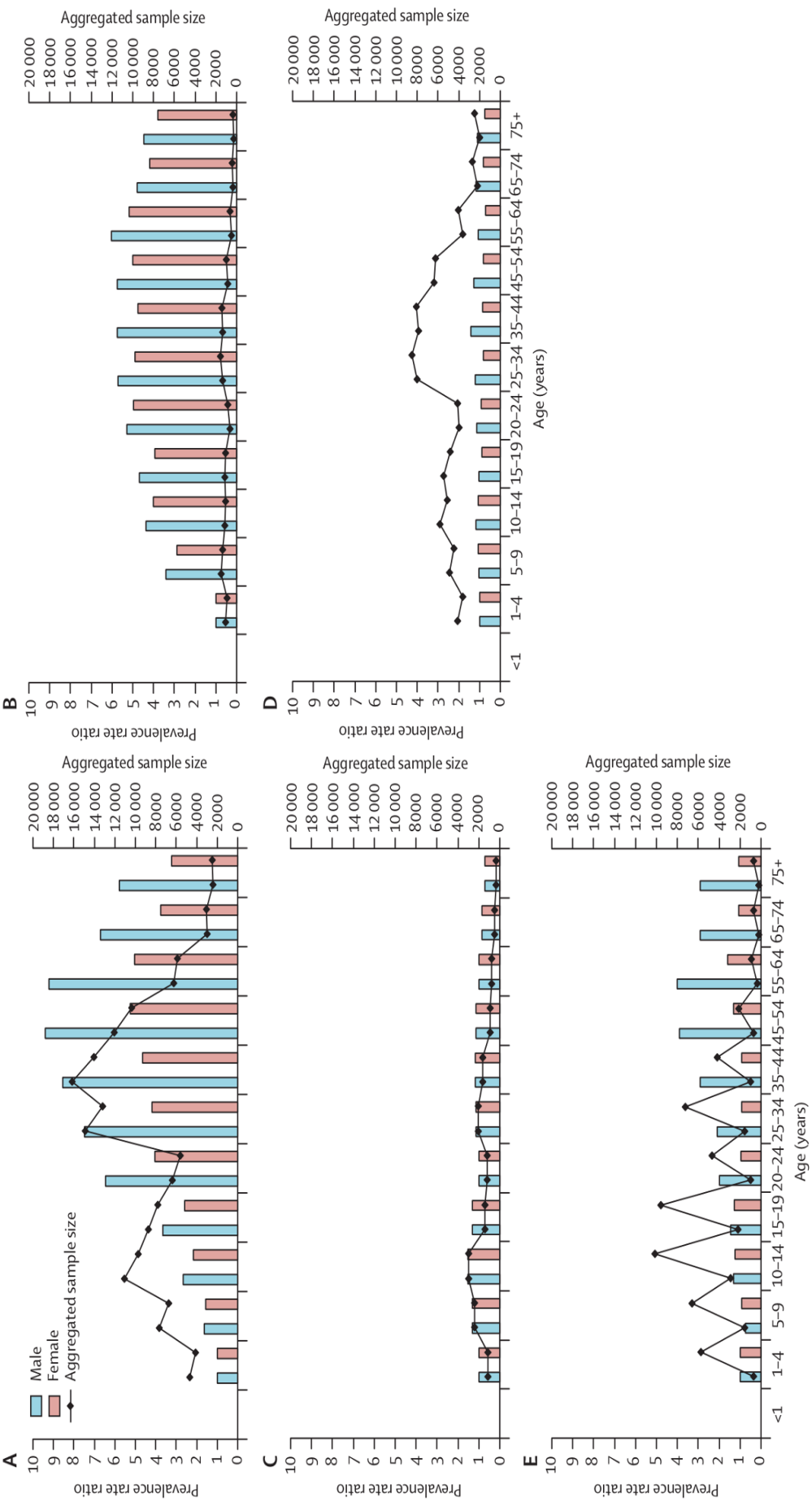

Figure 15. Standardised, sex-specific and age-specific prevalence profiles of food-borne trematodiasis. Clonorchiasis (A). Opisthorchiasis (B). Fascioliasis (C). Intestinal fluke infections (D). Paragonimiasis (E). Prevalences in age groups 1-4 years are set equal to one for both sexes for standardisation. The age profile for fascioliasis is the same for both sexes because of insufficient sex-specific age-group data. Bibliographic details on the references of the quantitative datasets included are provided in Appendix 13.2.3. und Appendix 13.2.4.

Table 12. Summary of parasite-specific and region-specific modelled point estimates for human food-borne trematodiasis in 2005, based on GBD 2010 study regions.

	Total number of infected	Number of heavy infections	Number of cerebral infections	Number of deaths	YLD	YLL	DALYs
Clonorchiasis							
Asia, east (China, Hong Kong, Macau)	12,905,956	948,585	NA	4,690	30,998	200,549	231,547
Asia, southeast (Vietnam)	1,247,370	98,276	NA	484	4,067	22,299	26,366
Asia Pacific, high income (South Korea)	1,157,013	84,876	NA	416	2,013	15,390	17,403
Europe, eastern (Russia)	2,879	245	NA	1	5	49	54
Global	15,313,218	1,131,982	NA	5,591	37,083	238,287	275,370
Opisthorchiasis							
Asia, southeast (Laos, Thailand)[a]	8,028,503	315,723	NA	1,323	11,003	63,067	74,070
Europe, eastern (Russia, Ukraine)[b]	325,160	12,682	NA	0	240	0	240
Asia, central (Kazakhstan)[b]	44,567	1,582	NA	0	57	0	57
Global	8,398,230	329,987	NA	1,323	11,300	63,067	74,367
Fascioliasis							
Latin America, Andean (Bolivia, Ecuador, Peru)	1,378,341	151,463	NA	0	17,318	0	17,318
North Africa or Middle East (Egypt, Iran)	1,119,812	133,268	NA	0	17,275	0	17,275
Asia, east (China)	144,427	14,310	NA	0	606	0	606
Europe, western (Portugal, Spain)	3,933	469	NA	0	7	0	7
Global	2,646,515	299,510	NA	0	35,206	0	35,206

Table 12. Continued.

	Total number of infected	Number of heavy infections	Number of cerebral infections	Number of deaths	YLD	YLL	DALYs
Intestinal fluke infections							
Asia, southeast (Philippines, Thailand)	3,392,726	477,319	NA	0	56,434	0	56,434
Asia, east (China)	2,691,606	353,805	NA	0	20,524	0	20,524
Asia Pacific, high income (South Korea, Japan)	596,586	88,855	NA	0	6,637	0	6,637
Europe, eastern (Russia)	28,790	4,147	NA	0	79	0	79
North Africa or Middle East (Egypt)	13,841	2,011	NA	0	25	0	25
Global	6,723,549	926,137	NA	0	83,699	0	83,699
Paragonimiasis							
Asia, east (China)	22,320,640	4,909,332	159,953	235	175,997	12,442	188,439
Latin America, Andean (Ecuador, Peru)	630,173	131,345	4,420	8	6,960	443	7,403
Asia, southeast (Laos)	203,334	43,876	1,467	1	780	87	867
Asia Pacific, high income (South Korea)	957	176	20	0	1	0	1
Global	23,155,104	5,084,729	165,860	244	183,738	12,972	196,710
All food-borne trematodiasis							
Global	56,236,616	7,772,345	165,860	7,158	351,026	314,326	665,352

Includes countries and special administrative regions with cases included in the estimates. Total number of infected, number of symptomatic cases, deaths, years lived with disability, years of life lost, and DALYs attributable to human food-borne trematodiasis are displayed for the different world regions in 2005. World regions are defined according to the GBD 2010 study guidelines.[1] DALYs are calculated without age-weighting or discounting (i.e., they represent so-called DALYs [0,0]). Lower and upper estimates based on 95% CIs and credible intervals are provided in Appendix 13.2.9. YLD = years lived with disability. YLL = years of life lost. DALY = disability-adjusted life years. NA = not applicable. [a]Only *Opisthorchis viverrini*. [b]Only *Opisthorchis felineus*.

6.5. Discussion

We estimate that in 2005 about 56.2 million people were infected with food-borne trematodes, 7.9 million had severe sequelae, and 7,158 died. Taken together, the global burden of food-borne trematodiasis was 665,352 DALYs. Importantly, food-borne trematode infections are also a disease of veterinary importance causing substantial losses in animal production and trade[9] and thereby affecting human well-being in indirect ways.

Several peculiarities of the initial model inputs and intermediate results in our study warrant further discussion. First, reliable prevalence data for calculating the global burden of food-borne trematodiasis were scarce. Because of the highly focal occurrences of these diseases,[9,13] localised small-scale surveys cannot directly serve as proxies for entire countries or larger regions (i.e., the 14 world regions defined by WHO). Hence, we decided to rely only on national prevalence data, despite the fact that many countries report some cases of food-borne trematodiasis but not on national totals.[51] In most countries, the few isolated surveys that have been done are not sufficient to be combined with other epidemiological information and remote sensing data in a geographical information system and successfully applied spatial statistical modelling techniques. Nevertheless, spatial modelling of fascioliasis has been attempted for Latin America[7,52] and similar approaches might be adopted for other settings and parasites in the future.

Second, most national prevalence rates included in our models were based on expert opinion and only a few on nationwide parasitological surveys. All prevalence rates based on nationwide surveys were established by coprology, except for that of paragonimiasis in China, where IgG ELISAs were used. These tests have a high sensitivity and a reasonable specificity.[53,54] Diagnostically relevant seroreversion occurs between 3 and 18 months,[55-57] with the delay presumably related to comparatively slow resolution of lesions containing antigenic material.[55] However, we cannot rule out a certain overestimation of paragonimiasis prevalence in China in our model. Other estimates for paragonimiasis in China are based on expert opinion and ranged between 0.078% and 1.73%, but explicitly refer to the national survey,[9,13,37] which also mentions that the number of paragonimiasis cases could increase in the future.[44] Measurement errors resulting from diagnostic limitations (e.g., confusion of paragonimiasis as non-responsive tuberculosis, non-detection or misdiagnosis of worm eggs in biospecimens)[3,5-8,10,13,26,54] might be common, but except for IgG ELISA they would lead to underestimates rather than overestimates.

Third, a few prevalence rates used in our study were from before 1995, and hence dating back more than 10 years to our estimation time point of 2005. Recent social and economic developments in endemic countries could have influenced the epidemiological situation of food-borne trematodiasis, but whether these changes resulted in enhanced or reduced risk of infection is unknown.[14] The high prevalence rates for *O. viverrini* in Thailand and Laos were expected, because the parasite is highly endemic in these two countries.[3,8-10,13,58]

Fourth, regarding sex-specific prevalence rates, many qualitative sources report that men are more often affected by clonorchiasis and opisthorchiasis and women by fascioliasis,[3,4,8,10,26,53] as confirmed in our models. No such qualitative evidence on differences in sex-related prevalence could be identified for intestinal fluke infections and paragonimiasis. For age-specific prevalence profiles of clonorchiasis and opisthorchiasis, the initial increase in prevalence in young individuals, a maximum in middle age, and a slight decrease in old age is frequently described,[3,8,10,59,60] and these prevalence profiles also occurred in our models. The slight decrease in prevalence in elderly people has sometimes been attributed to early death of infected individuals due to cholangiocarcinoma and other associated complications.[61] For fascioliasis, an increase in prevalence rates during childhood and a slight decrease in prevalence in adults has also been reported.[4,62] A potential explanation for the modelled equalised profile of intestinal fluke infections could be that various species were subsumed under this category, which in turn might have had a levelling-off effect. The profile of paragonimiasis might reveal a changing epidemiological situation. In poor regions, usually no paragonimiasis control efforts are in place and children catching and eating raw crustaceans while playing or helping their parents in agricultural activities are at highest risk of infection. In wealthier regions where control measures have been implemented for many years (e.g., Japan and South Korea), most cases are not in childhood, but rather in older age groups. However, many age-specific and sex-specific exceptions might exist due to local cultural habits.[6]

Fifth, comparatively high egg-count thresholds were applied to define heavy infections and therefore cases with severe sequelae attributable to food-borne trematodiasis. For instance, a threshold of 1,000 eggs per g of faeces was used for defining heavy cases of fascioliasis even though lower infection intensity cutoffs of 400 eggs per g of faeces were also used in other studies.[63] Because of missing information, thresholds were not adjusted for young age groups despite the fact that substantially lower worm burdens might be sufficient to cause severe disease in children and age-specific thresholds have already been used in the assessment of the global burden of intestinal nematode infections.[64] All light infections were

assumed to be asymptomatic because reliable quantitative data on the morbidity effect of infection duration or host susceptibility were not available. Hence, temporal effects such as the sometimes acute onset of *O. felineus* infection[3,8,10] and fascioliasis,[7,26,29,31,65] which might be prolonged and overlap with subsequent phases because of repetitive infections, were not assessed. Also subtle morbidity caused even by light infections, opportunistic infections (e.g., helminth infections and HIV/AIDS[66]), or sequelae with many sources such as anaemia, reduced physical fitness, and cognitive impairments could not be included in our estimates. Furthermore, the dependence of the simplified disease models on egg counts was an imperfect approximation because some studies questioned a direct relation between egg counts and worm burden. These studies showed irregular distribution of eggs in the faeces, obstructions in the hosts' organs, which could prohibit excretion of eggs, and crowding effects, which could reduce the egg production of each fluke.[26,39,40,59,67-69]

Sixth, other studies mention that about 5-10% of all clonorchiasis and opisthorchiasis cases might be heavy and symptomatic, which is comparable with our estimates.[8,23,41,70] For fascioliasis, 17.5% of patients could have massive infections and up to half of all patients could have clinical signs and symptoms.[71,72] No studies allowing for comparison could be identified for the diverse group of intestinal fluke infections. Reviews on paragonimiasis mention that 40-70% of all cases had pleural effusion and that about 80% of them might be symptomatic.[73-75] Another study done in Vietnam found that 80-100% of all lung-fluke infections were symptomatic.[76] Three reviews reported that cerebral involvement in all cases of paragonimiasis was about 1%,[30,77,78] which is similar to our findings, whereas older studies suggested much higher proportions, but due to selection of patients at hospital these studies most likely overestimated percentages.[79-81]

Seventh, our initial model assumption of zero remission was based on several factors. Food-borne trematodiases are neglected diseases, which primarily affect poor populations worldwide.[15] A recent review states that food-borne trematodiasis control efforts were inadequate in 2006, and only a few countries had large-scale efforts to control morbidity.[82] Indeed, this review estimates that coverage of food-borne trematodiasis control interventions is about 0.03%, and even when taking into account beneficial effects of other helminth control programmes the coverage would increase to just 0.3%. However, a single liver or lung fluke can live 10 years or more in a human host[4,6,10,31,59,83] if left untreated and only intestinal flukes have shorter life-spans (about 1-2 years).[28,84,85] Furthermore, re-infection is common after spontaneous or chemotherapeutic cure if they are not accompanied by integrated control efforts.[4,10,28,59-62,86-89] Heavily infected and therefore symptomatic cases are probably most

susceptible,[59,60] and heavy infections lasting for years lead to irreversible organ and tissue damage, which impairs patients' well-being even after parasite clearance.[90] Also, non-fatal cases of cerebral paragonimiasis usually present with long-term recurrent symptoms.[31,91,92] Chemotherapy might help only in the early phase of cerebral infection, and surgical removal of worms, eggs, and cerebral lesions are supportive measures in chronic infections.[6,91,92]

Eighth, odds ratios for cholangiocarcinoma with clonorchiasis and opisthorchiasis infections were comparable to the previously published odds ratios of 5.0 for both diseases.[93] The only population-based cross-sectional survey on *O. viverrini* and cholangiocarcinoma, which also assessed infection intensity, established an exposure-response relation with odds ratios ranging from 1.7 for infections with less than 1,500 eggs per g of faeces to 14.0 for infections with over 6,000 eggs per g of faeces.[35] No point of reference was identified for mortality caused by cerebral paragonimiasis, but since most patients might not have access to any treatment, death of about every tenth incident case seems possible for a brain infection.

Finally, as disability weights for sequelae of food-borne trematodiasis are not yet established, we had to rely on established disability weights of most similar sequelae from the GBD 2004 update[43] for the final burden estimation.

The modelled prevalence and mortality for the different food-borne trematode infections mostly follow the input data in our DisMod 3 models. Because we found no data on disease remission and duration, we assumed remission to be zero and duration was therefore implicitly defined as life-long. However, the ultimate DisMod 3 outputs represent conservative estimates with prevalences not always reaching the highest peaks of input data and remission rates higher than zero, especially in adults. The estimates for both parameters were nevertheless accepted to improve plausibility of all modelled parameters, and limited remission can be interpreted as spontaneous cure of some cases after a long period of infection, which seems plausible. Hence, the modelled incidence and all other output parameters are judged to be reliable and consistent even though good points of reference are not always available.

Our estimates for total number of infections (56.2 million) in 2005 are 35% higher than WHO figures for 1995.[9] For the same period (1995-2005), population figures from the GBD 2010 study showed an average population increase of only 8% in the countries and special administrative regions with cases included in the estimates. Compared with the aforementioned WHO figures for 1995, we reported an increase of 423% for intestinal-fluke infections, 119% for clonorchiasis, 12% for paragonimiasis, and 11% for fascioliasis, and a decrease of 19% for opisthorchiasis. We could not identify any comparable figures for the

number of people presenting with severe signs and symptoms, but WHO reported about 10,000 deaths attributable to food-borne trematodiasis in 1997.[94] Particularly, estimates for liver fluke-induced cholangiocarcinoma have been corrected upwards in recent years. In 1997, researchers at the International Agency for Research on Cancer estimated that only 800 cases of cholangiocarcinoma were attributable to liver-fluke infection in 1990,[95] which would translate into 800 liver fluke-associated deaths in our model. In 2002, the estimate was as high as 2,500 deaths,[96] whereas a recent review mentioned that well over 6,000 cases of cholangiocarcinoma might be induced by liver-fluke infections.[97] However, on the basis of the observation that almost all of the histologically confirmed cases of cholangiocarcinoma are related to *O. viverrini* infection in Khon Kaen, Thailand, realistic annual global estimates of cases of cholangiocarcinoma attributable to *O. viverrini* might be 8,000-10,000.[12,21] Furthermore, investigators of all previously mentioned studies labeled their estimates as conservative.[12,21,95-97] Because of the close relation between liver flukes and cholangiocarcinoma, Vatanasapt and colleagues[12] concluded that "the best way to control cholangiocarcinoma is to control liver flukes".

Our point estimate of DALYs in 2005 attributable to food-borne trematodiasis are preliminary results of the GBD 2010 study and will be juxtaposed with estimates for other diseases, injuries, and risk factors to improve consistency among all estimates before being released as final results. However, comparison of our estimates with currently available burden estimates for malaria and other neglected tropical diseases[15,98-102] confirms human food-borne trematodiases as an important group of globally neglected diseases (Table 13). Because of the highly focal occurrence of food-borne trematodes, they might even be a major public health threat in the most highly affected areas. Furthermore, as a result of inadequate sanitary conditions, culturally deeply rooted food habits in some areas and changing food preferences in other areas, and associated growth of aquacultural production, food-borne trematodiasis seems to be a cluster of emerging infectious diseases with over a billion people, mainly in the southeast Asian and western Pacific region, at risk of infection.[14]

Our estimates are likely to be only the tip of the iceberg. For instance, studies have reported 50 million intestinal fluke infections,[103] over 30 million *C. sinensis* and *Opisthorchis* spp. infections together,[104] and 17 million *Fasciola* spp. infections.[104] Uncertainty due to missing or incomplete data is also mirrored by the wide range between our lower (479,496 DALYs) and upper estimates (859,051 DALYs). Hence, the ultimate goal for future assessments of the burden of food-borne trematodiasis is to minimise the gap between actual and reported prevalences and between the complex natural histories of the diseases and

the simplified models as applied in our calculations. We therefore believe our study is a benchmark for future investigations and would like to invite readers to either send additional relevant information to us for inclusion in our models or prepare further analysis themselves. Our vision is to include all relevant information on human food-borne trematodiasis in the open-access Global Neglected Tropical Diseases Database (http://www.gntd.org) and to initiate similar documentation and control efforts as those under way for schistosomiasis (see for example http://www.eu-contrast.eu and http://score.uga.edu) or soil-transmitted helminthiasis (see for example http://www.thiswormyworld.org).

Table 13. Global disease burden of malaria and selected neglected tropical diseases, including food-borne trematodiasis.

Disease	Reference	Population at risk (millions)	People infected (millions)	People with morbidity (millions)	Deaths (thousands)	DALYs (thousands)
Malaria	[98,99]	2,211	NK	515	1,272	46,486
Neglected tropical diseases						
Hookworm infection	[100,101]	3,195	576-740	150	3-65	59-22,100
Ascariasis	[100,101]	4,211	807-1,221	350	3-60	1,817-10,500
Trichuriasis	[100,101]	3,212	604-795	220	3-10	1,006-6,400
Schisosomiasis	[101]	779	207	120	15-280	1,702-4,500
Lymphatic filariasis	[101]	>1,000	120	43	0	5,777
Trachoma	[98]	NK	150	NK	0	2,329
Leishmaniasis	[98,102]	350	12	NK	51	2,090
Trypanosomiasis	[98,102]	>60	0.5	NK	48	1,525
Chagas disease	[98,102]	120	11-18	NK	14	667
Food-borne trematodiasis	[14, a]	1,066	56.2	7.9	7.2	665
Onchocerciasis	[98,102]	120	18	NK	0	484
Leprosy	[98]	NK	NK	NK	6	199
Dracunculiasis	[15]	NK	NK	NK	NK	<100
Strongyloidiasis	[100]	NK	30-100	NK	NK	NK
Buruli ulcer	[15]	NK	NK	NK	NK	NK
Taeniasis and cysticercosis	[15]	NK	NK	NK	NK	NK

Estimates represent the population at risk, the number of people infected, the morbidity, the number of deaths, and the global burden as measured in disability-adjusted life years. DALYs = disability-adjusted life years. NK = not known. [a]Data mainly gathered from our study.

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6.8. References

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(Additional references are provided in a web reference list and shown in Appendix 13.2.3. and Appendix 13.2.4.)

7. Effect of schistosomiasis and soil-transmitted helminth infections on physical fitness of schoolchildren in Côte d'Ivoire

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7.1. Abstract

Background: Schistosomiasis and soil-transmitted helminthiasis are important public health problems in sub-Saharan Africa causing malnutrition, anemia, and retardation of physical and cognitive development. However, the effect of these diseases on physical fitness remains to be determined.

Methodology: We investigated the relationship between schistosomiasis, soil-transmitted helminthiasis and physical performance of children, controlling for potential confounding of *Plasmodium* spp. infections and environmental parameters (i.e., ambient air temperature and humidity). A cross-sectional survey was carried out among 156 schoolchildren aged 7-15 years from Côte d'Ivoire. Each child had two stool and two urine samples examined for helminth eggs by microscopy. Additionally, children underwent a clinical examination, were tested for *Plasmodium* spp. infection with a rapid diagnostic test, and performed a maximal multistage 20 m shuttle run test to assess their maximal oxygen uptake (VO_2 max) as a proxy for physical fitness.

Principal findings: The prevalence of *Schistosoma haematobium*, *Plasmodium* spp., *Schistosoma mansoni*, hookworm and *Ascaris lumbricoides* infections was 85.3%, 71.2%, 53.8%, 13.5% and 1.3%, respectively. Children with single, dual, triple, quadruple and quintuple species infections showed VO_2 max of 52.7, 53.1, 52.2, 52.6 and 55.6 ml kg^{-1} min^{-1}, respectively. The VO_2 max of children with no parasite infections was 53.5 ml kg^{-1} min^{-1}. No statistically significant difference was detected between any groups. Multivariable analysis revealed that VO_2 max was influenced by sex (reference: female, coef. = 4.02, $p < 0.001$) and age (years, coef. = 21.23, $p < 0.001$), but not by helminth infection and intensity, *Plasmodium* spp. infection, and environmental parameters.

Conclusion/Significance: School-aged children in Côte d'Ivoire showed good physical fitness, irrespective of their helminth infection status. Future studies on children's physical fitness in settings where helminthiasis and malaria co-exist should include pre- and post-intervention evaluations and the measurement of hemoglobin and hematocrit levels and nutritional parameters as potential co-factors to determine whether interventions further improve upon fitness.

Keywords: Schistosomiasis, soil-transmitted helminthiasis, *Plasmodium* spp., physical fitness, shuttle run test, Côte d'Ivoire.

7.2. Author summary

The burden of parasitic worm infections is considerable, particularly in developing countries. It is acknowledged that parasitic worm infections negatively impact on children's school performance and physical development. A deeper understanding of these linkages is important for updating burden of disease measures. We investigated the relationship between worm infection status and physical fitness of 156 schoolchildren from Côte d'Ivoire and controlled for potential confounding of *Plasmodium* infection (the causative agent of malaria) and environmental parameters (temperature and humidity). Children were diagnosed for parasitic worm and *Plasmodium* infections, examined by a physician, and participated in a 20 m shuttle run test to assess their maximal oxygen uptake (VO_2 max) as a proxy for physical fitness. Most of the children had parasitic worms and a *Plasmodium* infection. Nevertheless, their physical fitness was excellent (average VO_2 max: 52.7 ml kg^{-1} min^{-1}). The level of VO_2 max was only influenced by sex and age, but not by parasitic worms and *Plasmodium* infections. In future studies, the dynamics of children's physical performance should be assessed before and after control interventions, including the assessment of blood hemoglobin, hematocrit, and nutritional indicators to determine whether physical fitness in worm- and *Plasmodium*-infected individuals can be further improved.

7.3. Introduction

Neglected tropical diseases and malaria are widespread on the African continent and elsewhere in the developing world. These diseases predominantly plague the poorest of the poor and delay their social and economic development.[1-3] Infections with soil-transmitted helminths (*Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*) and schistosomes (*Schistosoma mansoni* and *S. haematobium*), for example, affect hundreds of millions of people with untold morbid sequelae.[4-6] Helminths parasitizing humans can destroy the organs and tissues in which they live and compete for nutrients with the human host. Consequently, infections can result in abdominal pain, diarrhea, intestinal obstruction, anemia, malnutrition, ulcers and, particularly in severe chronic and untreated infections, even death.[5,7-9] These sequelae, in a chronic stage, may retard children's physical development.[8,10,11] It is also hypothesized that helminth infections negatively impact on cognitive abilities, and hence on children's school performance.[12] However, some more recent studies could not find any clear association between helminth infections and school performance, and hence additional research is needed.[13-15]

To date, only few attempts have been made to quantify the effect of schistosomiasis and soil-transmitted helminth infections on children's physical fitness.[16,17] In the early stage of a schistosome infection, general fatigue is a common symptom described in various age groups.[18] As helminth infections progress, the intensity and duration is thought to play an important role in influencing physical fitness.[19] Hence, the assessment of infection intensities should be regarded as an important component of evaluating the effect of helmintic diseases on people's general health and well-being. In the light of the currently ongoing comprehensive revision of the global burden of diseases estimates[20,21] and the crucial role of disability weights, which are exceedingly difficult to estimate among the neglected tropical diseases,[22-24] the quantitative impact of helminth infections on humans' physical fitness deserves closer attention.

The aim of this study was to investigate whether or not there is a relationship between helminth infection status among school-aged children and their physical fitness. The study was carried out in Côte d'Ivoire, in an area highly endemic for schistosomiasis and, to a lesser extent, soil-transmitted helminthiasis, using a cross-sectional study type. Malaria is co-endemic, and hence we also determined *Plasmodium* spp. infections and controlled for environmental factors such as ambient air temperature and humidity.

7.4. Methods

7.4.1. Ethics statement

The study protocol was approved by the institutional research commission of the Swiss Tropical and Public Health Institute (Basel, Switzerland) and received clearance from the ‘‘Ethikkommission beider Basel’’ (EKBB, reference no. 377/09) and the Comité National d’Ethique et de la Recherche (CNER) in Côte d’Ivoire (no. 1993 MSHP/CNER). The study was covered by an insurance company (GNA Assurance; Abidjan, Côte d’Ivoire, policy no. 30105811010001). District health and education authorities, the village chief, parents/guardians, and schoolchildren were informed about the purpose, procedures, and potential risks and benefits of the study. Written informed consent was obtained from parents/guardians and children assented orally. Participation was voluntary and children could withdraw from the study anytime without further obligation. All results were coded and treated confidential. In some cases, where a need for medical intervention was required, the name of the individual was communicated to the local health service in order to provide appropriate medical follow-up. At the end of the study, all children attending the primary school of Grand Moutcho I, II and III were administered praziquantel (single 40 mg/kg oral dose) and albendazole (single 400 mg oral dose) free of charge, irrespective of the children’s helminth infection status.

7.4.2. Study design and sample size calculation

We conducted a cross-sectional survey on physical activity in schoolchildren. We assumed that the arithmetic mean of the maximal oxygen uptake (VO_2 max), which was measured as a proxy for the school-aged children’s physical fitness, would be 50 ml kg^{-1} min^{-1} with a standard deviation of 5 ml kg^{-1} min^{-1} (see σ in formula 1).[25] Moreover, we assumed that a difference of VO_2 max of 5% (i.e., 2.5 ml kg^{-1} min^{-1}; see D in formula 1) is of clinical relevance and that the ratio of children with the predominant helminth species *versus* non-infected children would be roughly 1:1. According to formula (1) given by Eng (2003)[26]

$$N = \frac{4 * \sigma^2 * (z_{crit} + z_{pwr})^2}{D^2} \qquad (1)$$

and allowing for 10% non-compliance, we calculated that 186 children in total would need to be enrolled to achieve a power of 90% at an alpha error of 5% to find a statistical significance in VO_2 max between helminth-infected and non-infected individuals. Finally, we aimed to enroll 200 children to account for imbalances in the study group sizes.

7.4.3. Study area and population

The study was carried out between January and April 2010 in the primary school Grand Moutcho, located in the health district of Agboville, south Côte d'Ivoire (geographical coordinates: 05°56'0'' N latitude, 04°13'0'' W longitude). The study area is located 76 km north of Abidjan, the economic capital of Côte d'Ivoire, at an altitude of below 100 m above sea level. In south Côte d'Ivoire, the vegetation primarily consists of rainforest, the relief is flat and the long and short rainy seasons occur between April and July and from mid-September to November, respectively. During the school year 2009/2010, there were a total of 204 children attending grades 4, 5, and 6 in Grand Moutcho II and III, and hence all of them were invited to participate in the study.

7.4.4. Field and laboratory procedure

Village authorities and teachers were informed about the purpose and procedures of the study. Subsequently, teachers were asked to prepare class lists with the name, age, and sex of the children attending grades 4-6 of Grand Moutcho II and III. After written informed consent was obtained from parents or guardians and children gave oral assent to participate, children were provided with plastic containers labeled with unique identification numbers and invited to submit a small portion of their own fresh morning stool the following day. Stool samples were collected between 08:00 and 10:00 hours and children were handed out a new empty container for urine collection starting at 10:00 hours. This procedure was repeated the following day in order to obtain two stool and two urine samples from each child.

Stool and urine samples were transferred to a nearby laboratory in the district town Agboville. For the diagnosis of *S. mansoni* and soil-transmitted helminth infections, duplicate Kato-Katz thick smears, using 41.7 mg templates,[27] were prepared from each stool sample and examined under a microscope by experienced laboratory technicians. The number of eggs was counted and recorded for each helminth species separately. For the diagnosis of *S. haematobium*, urine samples were subjected to the filtration method.[28,29] In brief, 10 ml of

vigorously shaken urine were pressed through a small-meshed filter (30 mm), a drop of lugol solution was added to the filter paper on the microscope slide, and the slides were examined quantitatively under a microscope for *S. haematobium* eggs by experienced technicians. Consistent with our previous work, 10% of the slides were re-examined by a senior technician[30,31] and, in case of disagreement, the results were discussed with the concerned technician and the corresponding samples read a third time and used as a reference.

7.4.5. Physical examination and shuttle run test

Children who had provided two stool and two urine samples were clinically examined by a physician three days after the laboratory examination and, based on observed signs and symptoms, checked for their general state of health. Additionally, a rapid diagnostic test (RDT) for malaria was performed (ICT ML01 malaria Pf kit; ICT Diagnostics, Cape Town, South Africa). Children with clinical malaria (defined as positive RDT plus recent history of fever), asthma (assessed by study physician using a stethoscope), anemia (assessed by study physician after pulling down of eyelid and noting pale color[32]), or dyspnea (assessed by study physician using a stethoscope), according to the physician's appraisal, were excluded from the subsequent fitness test as motivating them to reach their maximal physical capacity was considered as potentially harmful.

The aim of the physical fitness test was to measure children's aerobe capacity and maximal oxygen up-take, the so-called VO_2 max.[33] The maximal multistage 20 m shuttle run test[25,34,35] is considered to be reliable and valid and was therefore utilized to determine the maximal aerobic capacity of the schoolchildren. Seventeen groups with a maximum of 10 children per group were running one group after the other on three consecutive days between 08:30 and 11:30 hours and between 16:00 and 18:00 hours. While doing the 20 m shuttle run test, the maximal heart rate of participating children was assessed using a Polar RS400 watch (Polar Electro Europe BV; Zug, Switzerland) to ensure that children really tried to reach their maximal physical capacity. Achieving less than 180 heart beats per min was taken as criterion that a child did not perform the test until the physical capacity limit.

To guarantee the comparability of the physical tests and to minimize external influences, which might affect the different test series of the 20 m shuttle run, ambient air temperature and humidity were monitored with a thermometer and a hygrometer, respectively.

7.4.6. Statistical analysis

Parasitological data were double-entered and cross-checked in Access version 2007 (Microsoft Corp.; Redmond, WA, USA) and analyzed in STATA version 10.1 (STATA Corp.; College Station, TX, USA). The completed race distance (levels and shuttles) according to the 20 m shuttle run test were obtained from version 3.2 of the Team Beep Test 20 m software (RobJWood Designs; Mount Hawthorn, Australia).

For each child, the arithmetic mean of the helminth species-specific egg counts from the four Kato-Katz thick smears was calculated and multiplied by a factor 24 to obtain a standardized measure of infection intensity, expressed as eggs per gram of stool (EPG). Helminth infection intensities were classified into light, moderate, and heavy, according to World Health Organization (WHO) guidelines.[29,36] The upper limits of light and moderate infections were 100 and 400 EPG for *S. mansoni*; 2,000 and 4,000 EPG for hookworm; and 5,000 and 50,000 EPG for *A. lumbricoides*, respectively. *S. haematobium* egg counts were classified into light (<50 eggs/10 ml of urine) and heavy (≥50 eggs/10 ml of urine or visible hematuria).[36]

Physical fitness data were gathered and analyzed according to standard methodologies put forth in ‘‘The Guidelines for Exercise Testing and Prescription’’ from the American College of Sports Medicine (ACSM).[33] VO_2 max results were obtained by using the age-adjusted (X_1 = age in years) positive linear relation between the shuttle running speed (X_2 = speed in km/h) and VO_2 max as expressed by Léger & Mercier[25] in equation 2:

$$VO_2\ max = 31.025 - 3.248 * X_1 + 3.238 * X_2 + 0.1536 * X_1 * X_2 \quad (2)$$

Only those children who had complete data records (i.e., written informed consent, four Kato-Katz thick smears, two urine filtrations, a RDT for malaria, completed clinical examination and 20 m shuttle run test) were included in the final analysis. Arithmetic mean, χ^2 and t-test statistics, as well as univariate and multivariable regression analyses were employed to assess statistical significance ($p < 0.05$). Children with complete parasitological and clinical data, but no valid results from the physical fitness test due to exclusion in the clinical examination or an invalid maximum heart rate while completing the physical fitness test were included in an attrition analysis.

7.5. Results

7.5.1. Compliance and demographic results

All 204 schoolchildren attending grades 4-6 of Grand Moutcho II and III were invited to participate in the study. As shown in Figure 16, 200 children (98.0%) returned written informed consent sheets signed by their parents/guardians. Complete parasitological results (i.e., four Kato-Katz thick smears, two urine filtrations, and one RDT for malaria) were available from 188 children and they all took part in the clinical examination and were willing to perform the 20 m shuttle run test. Hence, the compliance rate was 92.2%. However, another 26 children were excluded from the 20 m shuttle run test according to the physician's judgment. Exclusion criteria were dyspnea (n = 14), clinical malaria (n = 9), anemia (n = 2), and asthma (n = 1). The remaining 162 children participated in the 20 m shuttle run test, but the results of six children were considered as invalid because of maximum heart rate below 180 heart beats per min. Hence, the final study cohort consisted of 156 children (76.5% of the initial 204).

The median age of the final study population was 12 years with a range of 7-15 years. However, most of the children were aged between 9 and 15 years (98.7%). The predominant age-group were 13-year-old (n = 39). There were more boys (n = 91) than girls (n = 65).

7.5.2. Physical fitness

The overall arithmetic mean of the VO_2 max values of the 156 children was 52.7 ml kg^{-1} min^{-1} (95% confidence interval (CI): 52.0-53.4 ml kg^{-1} min^{-1}) (Table 14). Extreme values (minimum and maximum) were at 40.5 and 60.6 ml kg^{-1} min^{-1}. While girls had a mean VO_2 max of 50.4 ml kg^{-1} min^{-1} (95% CI: 49.4-51.3 ml kg^{-1} min^{-1}), the respective value for boys was significantly higher at 54.4 ml kg^{-1} min^{-1} (95% CI: 53.5-55.2 ml kg^{-1} min^{-1}). The observed differences in mean VO_2 max values between girls and boys varied with age. In general, mean VO_2 max values gradually decreased with age; for boys it decreased from 56.8 ml kg^{-1} min^{-1} among 7-year-old to 48.8 ml kg^{-1} min^{-1} among those aged 15 years. The respective decrease in girls was from 54.2 to 44.7 ml kg^{-1} min^{-1}.

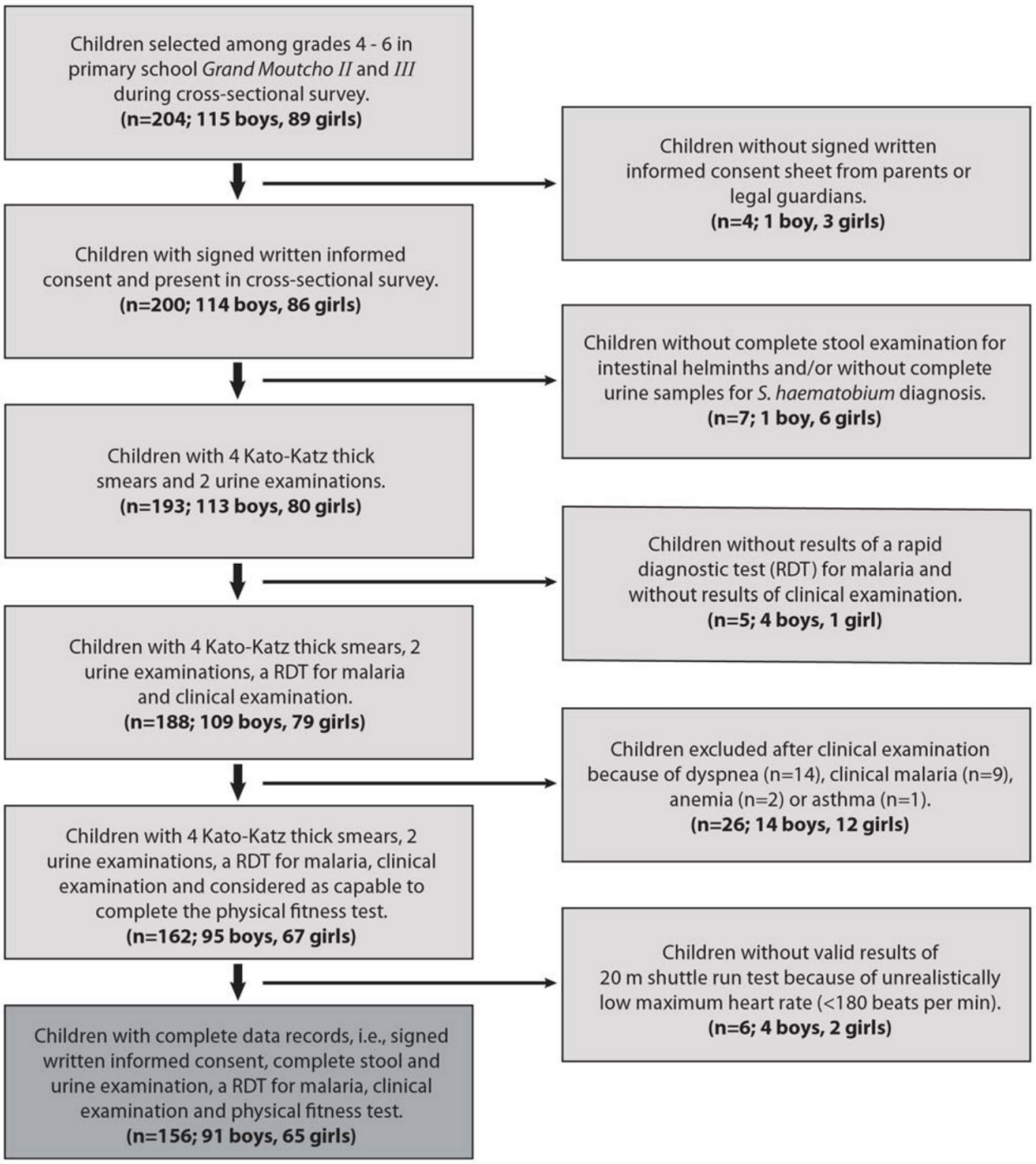

Figure 16. Study participation and compliance. Diagram showing the study participation and compliance of schoolchildren attending grades 4-6 of the primary school Grand Moutcho II and III, near Agboville, a rural community of south Côte d'Ivoire in early 2010.

Table 14. Comparison of age- and sex-specific mean VO_2 max values among Ivoirian and Canadian children.

Age	Sex	Agboville, Côte d'Ivoire, 2010			Québec, Canada, 1981		
Years		n	Mean VO_2 max	95% CI	n	Mean VO_2 max	95% CI[a]
7	M	2	56.8	15.7-97.9	297	51.2	50.9-51.6
	F	0	NA	NA	299	50.3	50.0-50.6
8	M	0	NA	NA	303	51.7	51.2-52.1
	F	0	NA	NA	308	49.8	49.4-50.2
9	M	5	55.9	53.3-58.4*	322	51.1	51.1-52.0*
	F	6	54.2	52.2-56.1*	322	49.2	48.9-49.6*
10	M	12	56.0	53.3-58.8*	404	51.6	51.2-52.1*
	F	14	53.8	52.0-55.6*	335	46.8	46.5-47.1*
11	M	9	56.3	53.9-58.8*	386	51.1	50.7-51.6*
	F	7	50.2	47.1-53.3	382	47.5	47.1-47.9
12	M	24	54.5	53.0-56.0*	341	51.9	51.4-52.5*
	F	9	50.2	47.9-52.5*	292	46.7	46.2-47.1*
13	M	22	54.4	52.8-55.9*	325	50.1	49.5-50.7*
	F	17	48.4	47.0-49.8*	298	44.4	43.9-45.0*
14	M	10	52.9	50.5-55.3	289	50.1	49.5-50.7
	F	8	48.9	45.7-52.1*	260	41.7	41.1-42.2*
15	M	7	48.8	42.9-54.7	333	50.2	49.6-50.9
	F	4	44.7	39.0-50.3	260	41.2	40.5-41.8
7-15	M	91	54.4	53.5-55.2	3,000	51.1	NA
7-15	F	65	50.4	49.4-51.3	2,756	46.6	NA
7-15	Both	156	52.7	52.0-53.4	5,756	48.9	NA

VO_2 max values (expressed in ml kg^{-1} min^{-1}) were obtained from 20 m shuttle run tests performed by 156 children attending grades 4-6 in the primary school of Grand Moutcho II and III near Agboville, south Côte d'Ivoire in early 2010 (present study) and from children in Québec, Canada, in 1981. CI = confidence interval. F = female. M = male. NA = not applicable. [a]Values calculated by authors of the present article, based on data in Léger *et al.* (1988).[25] *Statistically significant difference between the two studies according to non-overlapping 95% CI.

7.5.3. Parasitological characteristics in relation to VO_2 max

Prevalence and infection intensity of helminth and *Plasmodium* spp. infections, stratified by age and sex, are summarized in Table S1 (Appendix 13.3.1.). Overall prevalences for *S. haematobium*, *Plasmodium* spp., *S. mansoni*, hookworm and *A. lumbricoides* were 85.3%, 71.2%, 53.8%, 13.5% and 1.3%, respectively. No eggs of *T. trichiura* were identified, whereas eggs of *Hymenolepis diminuta* were found in the stool of one child.

Among the 133 children infected with *S. haematobium*, 57.9% carried light and 42.1% heavy infections. The arithmetic mean egg count was 52 eggs/10 ml of urine (range: 1-346 eggs/10 ml of urine). Among the 84 *S. mansoni*-infected children, 64.3% presented with light, 32.1% with moderate, and 3.6% with heavy infection intensity. The arithmetic mean fecal egg count (FEC) of all *S. mansoni*-infected children was 116 EPG (range: 6-852 EPG). All 21 hookworm infections were diagnosed as light, with an arithmetic mean FEC of 42 EPG (range: 6-120 EPG). Only one light (4,668 EPG) and one moderate (11,226 EPG) *A. lumbricoides* infection was detected.

VO_2 max values of children with a *S. haematobium*, *S. mansoni*, hookworm or *A. lumbricoides* infection were 52.5, 52.2, 54.8 or 52.3 ml kg^{-1} min^{-1}, respectively, whereas children without helminth infection showed a mean VO_2 max of 52.9 ml kg^{-1} min^{-1} (Table 15). Multi-parasitism was very common. While only 3.8% of all children were neither infected with helminths nor with *Plasmodium* spp., 16.7% harbored one, 35.9% two, 38.5% three, 4.5% four and 0.6% even five parasite species concurrently. Children with single, dual, triple, quadruple and quintuple species infections showed VO_2 max values of 52.7, 53.1, 52.2, 52.6 and 55.6 ml kg^{-1} min^{-1}, respectively. The exact parasite combinations and respective VO_2 max values are presented in Table 16.

However, as demonstrated by overlapping 95% CIs in Tables 15 and 16, no significant differences were found in the VO_2 max values of helminth-infected and non-infected children, regardless of the helminth species investigated, regardless of whether children were infected with one or multiple species concurrently, and regardless of the helminth infection intensity. The results of the two parasites with the most diverse infection intensities, as measured by the number of eggs in a given amount of urine or stool, namely *S. haematobium* and *S. mansoni*, were used to illustrate their effect on the children's VO_2 max. As documented in Figure 17, no clear trend was observable.

Table 15. Helminth infection intensities in accordance with WHO guidelines[36] and mean VO_2 max values.

Infection	Intensity	n	VO_2 max	
			Mean	95% CI
No helminth infection	NA	17	52.9	51.1-54.7
S. haematobium	All	133	52.2	51.8-53.4
	Light (<50 eggs/10 ml of urine)	77	52.8	51.8-53.8
	Heavy (≥50 eggs/10 ml of urine or visible hematuria)	56	52.2	50.9-53.5
S. mansoni	All	84	52.2	51.1-53.3
	Light (1-99 EPG)	54	52.8	51.4-54.2
	Moderate (100-399 EPG)	27	51.2	49.3-53.1
	Heavy (≥400 EPG)	3	51.4	37.0-65.8
Hookworm	All	21	54.8	52.8-56.8
	Light (1-1,999 EPG)	21	54.8	52.8-56.8
	Moderate (2,000-3,999 EPG)	0	NA	NA
	Heavy (≥4,000 EPG)	0	NA	NA
A. lumbricoides	All	2	52.3	10.4-94.2
	Light (1-4,999 EPG)	1	55.6	NA
	Moderate (5,000-49,999 EPG)	1	49.0	NA
	Heavy (≥50,000 EPG)	0	NA	NA

VO_2 max values (expressed in ml kg^{-1} min^{-1}) were achieved from 20 m shuttle run tests performed by 156 children attending grades 4-6 in the primary school of Grand Moutcho II and III near Agboville, a rural community of south Côte d'Ivoire in early 2010. CI = confidence interval. EPG = eggs per gram of stool. NA = not applicable.

Table 16. Multiparasitism and associated mean VO_2 max values.

Infection	Parasites	No. of observations (%)	VO_2 max	
			Mean	95% CI
No parasite infection	NA	6 (3.8)	53.5	49.6-57.4
Single infections	All single infections	26 (16.7)	52.7	51.4-54.0
	S. haematobium	13 (8.3)	53.1	51.5-54.7
	S. mansoni	2 (1.3)	50.9	8.2-93.5
	Plasmodium spp.	11 (7.1)	52.5	50.2-54.9
Double infections	All double infections	56 (35.9)	53.1	51.9-54.3
	S. haematobium and *S. mansoni*	17 (10.9)	53.1	50.6-55.6
	S. haematobium and hookworm	2 (1.3)	51.7	36.3-67.1
	S. haematobium and *Plasmodium* spp.	34 (21.8)	52.8	51.4-54.3
	S. mansoni and hookworm	1 (0.6)	60.6	NA
	S. mansoni and *Plasmodium* spp.	1 (0.6)	52.6	NA
	Hookworm and *Plasmodium* spp.	1 (0.6)	58.2	NA
Triple infections	All triple infections	60 (38.5)	52.2	50.8-53.5
	S. haematobium , *S. mansoni* and hookworm	3 (1.9)	54.2	36.2-72.2
	S. haematobium , *S. mansoni* and *A. lumbricoides*	1 (0.6)	49.0	NA
	S. haematobium , *S. mansoni* and *Plasmodium* spp.	50 (32.1)	51.5	50.1-53.0
	S. haematobium , hookworm and *Plasmodium* spp.	5 (3.2)	57.1	53.0-61.5
	S. mansoni , hookworm and *Plasmodium* spp.	1 (0.6)	56.9	NA
Quadruple infections	All quadruple infections	7 (4.5)	52.6	48.4-56.9
	S. haematobium , *S. mansoni* , hookworm, and *Plasmodium* spp	7 (4.5)	52.6	48.4-56.9
Quintuple infections	All quintuple infections	1 (0.6)	55.6	NA
	S. haematobium , *S. mansoni* , hookworm, *A. lumbricoides* and *Plasmodium* spp.	1 (0.6)	55.6	NA

VO_2 max values were obtained from 20 m shuttle run tests performed by 156 schoolchildren from the primary school in Grand Moutcho, Agboville, Côte d'Ivoire, in early 2010. CI = confidence interval. NA = not applicable.

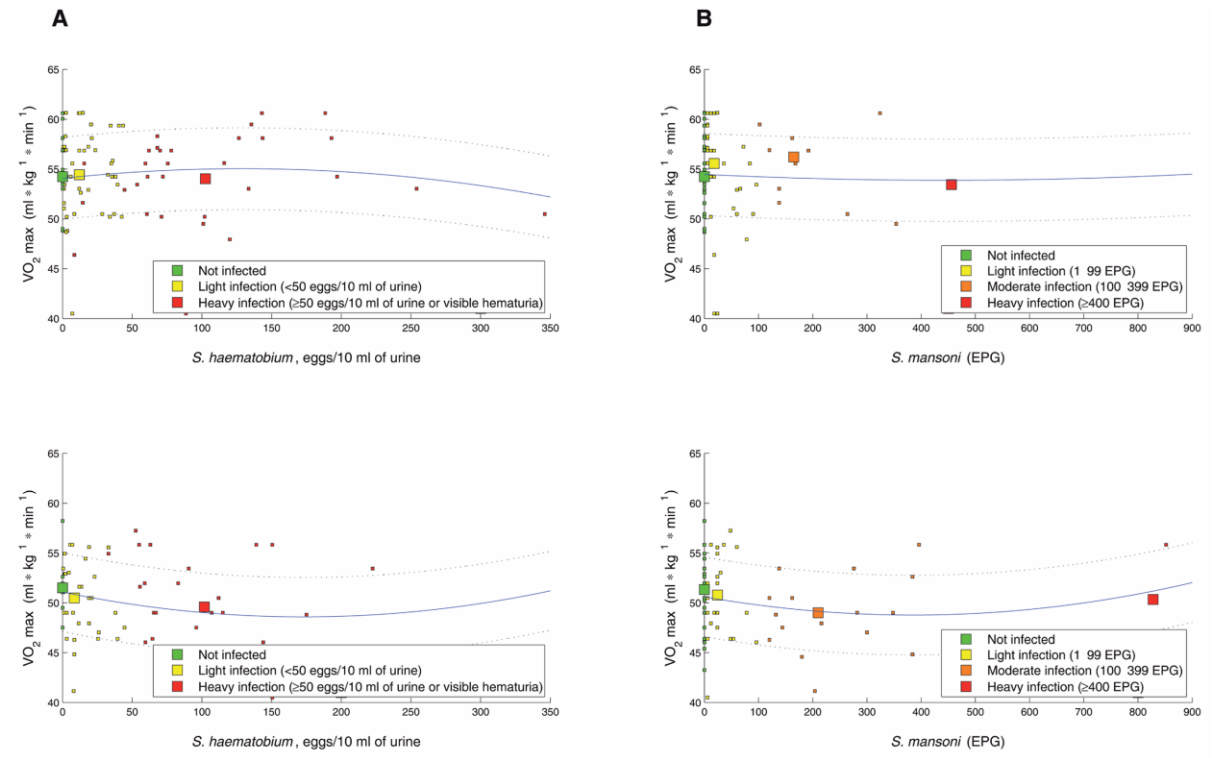

Figure 17. Sex-specific scatter plots of VO_2 max values among Ivoirian schoolchildren. VO_2 max values were obtained from 156 children attending grades 4-6 in the primary school of Grand Moutcho II and III near Agboville, south Côte d'Ivoire, in early 2010 after performing a 20 m shuttle run test. Data are shown in accordance with children's infection status of *S. haematobium*, measured in number of eggs per 10 ml of urine (A), and *S. mansoni*, measured in number of eggs per gram of stool (EPG) (B). Scatter plots on the top represent males and scatter plots on the bottom females. Second order polynomial regression lines (solid lines) and their 95% confidence intervals (dotted lines) are presented.

7.5.4. Mutlivariable regression analyses with physical fitness as outcome

A multivariable regression analysis supported our findings from the descriptive statistics. After adjusting for temperature (range: 31-43°C) and relative humidity (range: 42-69%) of the ambient air (measures taken when the children performed the physical activity test), sex and age, differences in VO_2 max values between children with differing parasitic infection status were not statistically significant (Table 17). The only statistically significant explanatories remained sex (reference: female, coeff. = 4.02, $p < 0.001$) and age (coeff. = -1.23, $p < 0.001$). These findings were robust and whether we used helminth infection intensity categories as defined by WHO or exact FECs had no influence on the outcome of the multivariable regression model.

Table 17. Multivariable regression analysis between VO_2 max values and air temperature, humidity, sex, age, and infection status as explanatory variables.

Explanatory variables	Multivariable regression analysis[a]		
	Coef.	95% CI	p-value
Air temperature (in °C)	0.33	-0.16–0.83	0.185
Relative humidity of the air (in %)	0.09	-0.13–0.31	0.404
Sex (reference: female)	4.02	2.83–5.21	<0.001*
Age (in years)	-1.23	-1.56– -0.89	<0.001*
Malaria (reference: not infected)	-0.02	-1.31–1.26	0.973
Helminth infection (reference: not infected)			
S. haematobium: light infection	-2.18	-10.37–6.00	0.599
S. haematobium: heavy infection	-2.11	-10.45–6.23	0.618
S. mansoni: light infection	-1.57	-9.52–6.38	0.697
S. mansoni: moderate infection	-2.49	-10.34–5.36	0.532
S. mansoni: heavy infection	-2.59	-11.35–6.16	0.559
Hookworm:light infection	1.14	-6.36–8.64	0.764
No. of concurrent helminth infections (reference: 0)			
One	3.95	-4.41–12.30	0.352
Two	5.33	-10.46–21.12	0.506
Three	4.90	-17.63–27.42	0.668

VO_2 max (ml kg^{-1} min^{-1}) values resulting from 20 m shuttle run tests performed by 156 children attending grades 4-6 in the primary school of Grand Moutcho II and III near Agboville, a rural community of south Côte d'Ivoire in early 2010. Only explanatories with n > 1 observations were included. CI = confidence interval. [a]Key indicators of the multivariable regression model: F (14, 140) = 8.20; p < 0.001; R-squared = 0.450. *Statistically significant (p < 0.05).

7.5.5. Attrition analysis

Characteristics of the 32 children with complete parasitological and clinical data, but no results from the physical fitness test were compared with the 156 children comprising the final study sample. This attrition analysis revealed that the two groups were similar with regard to the proportions of girls (43.8% *vs*. 41.7%) and mean age (11.7 *vs*. 12.0 years). No statistically significant differences in helminth infection intensity categories were detected for *S. haematobium*, *S. mansoni*, hookworm and *A. lumbricoides* (all p > 0.05), and occurrence of multiple helminth infections was comparable (p = 0.928) in both groups.

7.6. Discussion

Only few attempts have been made to determine the effect of schistosomiasis and soil-transmitted helminth infections on children's physical performance, which is closely related to their general health and well-being, and hence a proxy measure of disability and disease burden. We investigated the relationship between helminth infection status and physical fitness in schoolchildren from Côte d'Ivoire and controlled for potential confounding of malaria and environmental influences. *Schistosoma* spp. and *Plasmodium* spp. infection were present in more than two thirds of the surveyed children with 37.2% of the children concurrently infected with both *S. haematobium* and *S. mansoni*. Hookworm infections were also common. However, neither single infections with any investigated parasite species at any infection intensity, nor multiple species infections were associated with the maximal oxygen uptake VO_2 max, which is a widely used parameter to determine and quantify physical fitness. VO_2 max was only significantly related to children's age and sex and our cohort of children from Côte d'Ivoire presented with better physical fitness than children of the same age and sex in Canada.

Our data confirm previous studies showing that schistosomiasis and soil-transmitted helminthiasis are highly endemic in the Agboville area in south Côte d'Ivoire.[37-40] Interestingly, we found that children's physical activity in the current epidemiological setting of Côte d'Ivoire was, on average, considerably better than that of a large group of children from Canada. Indeed, the mean VO_2 max, among our cohort of children was 52.7 ml kg^{-1} min^{-1}, whereas a lower mean VO_2 max (48.9 ml kg^{-1} min^{-1}) had been observed in the aforementioned Canadian study.[25] Generally, schoolchildren in Grand Moutcho had a 3-7 ml kg^{-1} min^{-1} higher VO_2 max than their age-matched Canadian counterparts (Table 14), which corresponds to a positive overall offset of about 8%, despite the fact that the Ivorian children were running during high ambient air temperatures (up to 43°C) on an unpaved schoolyard and some of them had only sandals or no shoes at all. Moreover, we could not find evidence that a helminth of *Plasmodium* infection, multiple species helminth infections, and heavy helminth infection intensities negatively impact on children's performance in a 20 m shuttle run test. Our findings are in contrast to two Kenyan studies published in the early 1990s,[16,17] but in line with other investigations carried out in the 1970s,[11,41,42] and therefore raise the question as to why there is discrepancy between the widely held view that schistosomiasis and soil-transmitted helminthiasis prejudices physical fitness and the lack of consistent empirical data to support this claim.

The following points are offered for consideration. First, children in Grand Moutcho walk to school, day after day, often for several kilometers. Moreover, children are engaged in daily family chores, such as fetching water, help with subsistence agriculture and other physically demanding tasks. Compared to industrialized countries, where physical inactivity and other life-style modifiers have become important risk factors for ill-health,[43-45] children living in rural parts of Africa still show high levels of physical activity. Second, what might also contribute to an increased fitness level of children in Africa is their potentially lower protein and fat intake compared to children in developed countries.[46] Hence, a limitation of our study is that neither nutritional parameters nor hemoglobin nor hematocrit levels of participating children were assessed. Third, according to Åstrand & Ryhming (1954),[47] neither sex nor anthropometric measures are significant predictors for physical fitness test results. In the present study, however, sex was associated with VO_2 max with boys showing a statistically significantly higher mean value than girls. Moreover, there was a negative correlation between age and VO_2 max capacity in the examined children. Fourth, children are at highest risk of helminth infections and, at the same time, easier to motivate for participation in a physical performance test than adults. This latter fact may also explain the relatively high voluntary compliance rate of 92.2% (i.e., 188 out of 204). Fifth, children attending school might not be fully representative for a specific epidemiological setting, as school-aged children from the poorest and furthest away households are less likely to be registered at school. These children might be at a higher risk of helminth and *Plasmodium* infections. Sixth, it is conceivable that those children suffering from a heavy helminth infection or clinical malaria rest at home because of abdominal pain, nausea or headache, and hence were absent at the time of the study. Seventh, an attrition analysis of the 32 children who had complete parasitological and clinical data but were excluded from the physical fitness test due to medical complaints (n = 26) or unreasonably low pulse rate (n = 6) revealed that they were not significantly different from the 156 included children in terms of sex, age, or parasite infection status. Nevertheless, 29 of the 32 children harbored at least one of the helminth species investigated, and hence it is possible that we excluded at least some individuals who suffered from severe disabilities attributable to their helmintic infections and thereby introduced a certain bias. Finally, our assumptions in the sample size calculation proofed to be too optimistic and mainly due to the unexpected high number of children, who had to be excluded from the physical fitness test because of medical complaints, the intended sample size could not be reached.

Currently, the results of the present study may support expert opinion that had assigned a minuscule disability weight for schistosomiasis, i.e., 0.005 for children aged 5-14 years and 0.006 for individuals aged 15 years and above on a scale from 0 (no disability) to 1 (death). These tiny disability weights, regardless of the schistosome species and infection intensity, are at the root of the low global burden estimate due to schistosomiasis, which, nonetheless, remains a heavily contested issue.[6,48-50] Based on our findings one might indeed challenge the effect of a helminth infection on physical performance of school-aged children. Due to the lack of advanced chronic disease in this age group, low disability weights might be justified. However, schistosome infections that remain untreated ultimately lead to chronic morbid sequelae in later life, and hence the current emphasis on regular administration of anthelmintic drugs to entire at-risk populations is reasonable.[51,52]

Future efforts to further investigate the often subtle disabling effects of helminth infections are still needed, as the previous elaborations manifest. Hence, it would be interesting to investigate the dynamics of children's physical fitness in a pretest-posttest design with an intermittent treatment, or, even better, within the frame of continuous preventive chemotherapy campaigns, which was not feasible in the present study due to administrative and organizational constraints in the field. Such surveys should also apply quantitative tests instead of RDTs to diagnose *Plasmodium* species-specific infection intensities (i.e., thick and thin blood films for parasitemia appraisal) and consider nutritional status as well as hemoglobin values as potential co-factors influencing individual physical fitness. They could again use a similar maximal physical capacity test like the one used in this study and which had the advantage that a group of children could be processed at once without the requirement of any sophisticated equipment. However, to avoid the aforementioned problem that a large number of individuals suffering from the most severe attributable disabilities have to be excluded due to potentially harmful exertion, one could also think of low intensity physical fitness tests using, for example, pedo-, speedo- and/or accelerometers. In recent years, such high-quality measuring instruments have become available and handy, and they have been used extensively and reported as valid objective measures of physical activity.[53] The results of studies adhering to such further elaborated protocols could help to shed light on the true health consequences incurred by single and – hitherto even more neglected – multiple helminth species infections.[54] By assisting in the definition of appropriate disability weights for global burden of diseases calculations, such data would directly improve key stakeholders knowledge-base, and hence enable them to take well-informed decisions about future priority setting in the public health agenda.

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8. Questionnaire-based approach to assess schoolchildren's physical fitness and its potential role in exploring the putative impact of helminth and *Plasmodium* spp. infections in Côte d'Ivoire

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8.1. Abstract

Background: Disability weights (DWs) are important for estimating burden of disease in terms of disability-adjusted life years. The previous practice of eliciting DWs by expert opinion has been challenged. More recent approaches employed quality of life (QoL) questionnaires to establish patient-based DWs, but results are ambiguous.

Methods: In early 2010, we administered a questionnaire pertaining to physical fitness to 200 schoolchildren in Côte d'Ivoire. Helminth and *Plasmodium* spp. infections were determined and schoolchildren's physical fitness objectively measured in a maximal multistage 20 m shuttle run test. Associations between objectively measured and self-reported physical fitness and between self-reported physical fitness and infection status were determined. Spearman rank correlation coefficient, uni- and multivariable linear regression models adjusting for children's age and sex, ambient air temperature and humidity, Fisher's test, χ^2 and t-test statistics were used for statistical analysis.

Results: The prevalence of *Schistosoma haematobium*, *Plasmodium* spp., *Schistosoma mansoni*, hookworm and *Ascaris lumbricoides* in 167 children with complete parasitological results was 84.4%, 74.9%, 54.5%, 14.4% and 1.2%, respectively. High infection intensities and multiple species parasite infections were common. In the 137 children with complete data also from the shuttle run test, we found statistically significant correlations between objectively measured and self-reported physical fitness. However, no statistically significant correlation between the children's parasitic infection status and self-reported physical fitness was identified. An attrition analysis revealed considerably lower self-reported physical fitness scores of parasitized children who were excluded from shuttle run testing due to medical concerns in comparison to parasitized children who were able to successfully complete the shuttle run test.

Conclusions: Our QoL questionnaire proofed valid to assess children's physical fitness in the current study area. Reasons why no differences in self-reported physical fitness in children with different parasitic infections were found are manifold, but do not preclude the use of QoL questionnaires in the elicitation of DWs. Indeed, the questionnaire was particularly useful in assessing physical fitness of those children, who were – supposedly due to parasitic infections – unable to complete the shuttle run test. Hence, we encourage others to use QoL questionnaires to determine not only physical fitness, but also more subtle morbidities.

Keywords: Schistosomiasis, soil-transmitted helminthiasis, *Plasmodium* spp., physical fitness, shuttle run test, questionnaire, quality of life, Côte d'Ivoire.

8.2. Background

The current revision of the Global Burden of Diseases, Injuries and Risk Factors (GBD) 2010 study has sparked new interest in quantifying disability attributable to all kinds of diseases, injuries and risk factors.[1] A crucial variable to estimate the GBD in terms of disability-adjusted life years (DALYs) is the disability weight (DW); a measure which ranges between 0 (perfect health) and 1 (death). Indeed, DWs should capture the disability incurred by an average case suffering from a specific sequela.[2] Of note, DWs are complementary to the utility weights used in the earlier but related quality-adjusted life years (QALYs) metrics.[3,4] In the initial GBD 1990 study, DWs were assessed by person trade-off exercises assigned to panels of public health experts.[2] This dependence on theoretical contemplation was one important source of criticism on the DALY metrics.[4-7] Hence, different research groups started to use one of the growing number of quality of life (QoL) questionnaire tools to estimate patient-based proxies for DWs for a wide range of health impairments[8] – amongst them the often subtle and therefore particularly difficult to elicit morbidity caused by neglected tropical diseases (NTDs). While some results indicate that QoL is significantly lower among individuals affected by NTDs compared to their non-affected counterparts,[9,10] others do not.[11] These conflicting findings might reflect the early state of research investigating the relationship between QoL and NTDs, and hence the need for further scientific inquiry has been emphasised.[12,13] However, the ambiguity of this early research also raises questions about the reliability and validity of a questionnaire-based approach in the assessment of impairments in QoL due to NTDs.

We used data from a cross-sectional survey pertaining to schoolchildren's helminth and *Plasmodium* spp. infections, as determined by standardised, quality-controlled parasitological methods. The data were juxtaposed to children's physical fitness, as objectively measured in a maximal multistage 20 m shuttle run test. Additionally, children's self-reported physical fitness was obtained by means of a QoL questionnaire. We determined associations between objectively measured and self-reported physical fitness on one hand, and self-reported physical fitness and infection status on the other hand. Particular emphasis was placed on physical fitness as it is a crucial dimension of QoL. Indeed, physical fitness is included in all generic QoL questionnaires[14-16] and, in our view, the dimension of QoL that can be most easily assessed objectively. We present an evaluation of a QoL questionnaire focusing on the dimension of physical activity. This tool was embedded in a cross-sectional epidemiological

survey, which aimed at assessing the effect of helminth and *Plasmodium* spp. infections on schoolchildren's physical fitness in a rural setting of southern Côte d'Ivoire.[17]

8.3. Methods

8.3.1. Study area and data collection

In early 2010, we invited all 204 schoolchildren attending grades 4-6 of Grand Moutcho primary school in Agboville, south Côte d'Ivoire, to participate in a cross-sectional epidemiological survey. In a first step, district health and education authorities, village leaders and teachers were informed about the purpose, procedures and potential risks of the study. After obtaining their oral agreement, written informed consent was sought from the parents or legal guardians of the children, whereas children assented orally.

In a next step, children were asked to fill out a brief questionnaire, assisted by their class teachers if needed. The questionnaire was based on two sections about physical functioning (PF) and physical role (PR) from the most widely used generic SF-36v2 questionnaire (Medical Outcome Trust, Boston, MA, USA; Health Assessment Lab, Boston, MA, USA; QualityMetric, Lincoln, RI, USA).[8,14,18] Fourteen questions were included and readily adapted to the specific study setting. The questionnaire was pre-tested with support of the head of the school and further revised (Appendix 13.4.1. Additional material. Questionnaire used to assess self-reported physical fitness in the present study; in French).

Next, participating children were given plastic containers and invited to submit, on the next day, a small portion of their fresh morning stool. After stool collection, from 10:00 hours onwards, children were given a second plastic container and asked to bring a urine sample by 14:00 hours the latest. This procedure was repeated over two consecutive days. Stool and urine samples were transferred to the nearby hospital laboratory of the district town Agboville. Duplicate Kato-Katz thick smears were prepared from each of the two stool samples and quantitatively examined by experienced laboratory technicians for eggs of *Schistosoma mansoni* and soil-transmitted helminths (i.e., *Ascaris lumbricoides*, hookworm and *Trichuris trichiura*) on the same day.[19] Urine samples were subjected to the filtration method and the number of *Schistosoma haematobium* eggs in a filtrate of 10 ml of urine counted under a microscope.[20,21] Ten percent of all parasitological results were re-examined by a senior technician for quality control. In case of disagreement with initial findings, the results were

discussed with the respective technician and the corresponding sample reanalyzed until agreement was reached.

After the helminthological screening, children were clinically examined by a physician to check their general state of health. Additionally, a rapid diagnostic test (RDT) for malaria was performed (ICT ML01 malaria Pf kit, ICT Diagnostics; Cape Town, South Africa). Children with clinical malaria (defined as positive RDT plus recent history of fever), asthma (assessed by stethoscopy), anaemia (assessed by observing conjunctival vasculature[22]) or dyspnoea (assessed by stethoscopy), according to the physician's appraisal, were excluded from the subsequent fitness test, as participation was considered potentially harmful to them.

Finally, all remaining children were invited to participate in a maximal multistage 20 m shuttle run test to assess the cumulatively covered distance and the aerobe capacity, as measured by their maximal oxygen uptake, the so-called VO_2max (expressed in ml kg^{-1} min^{-1}).[23,24] The shuttle run test was conducted in groups of not more than 10 children. The obtained results were used as objectively determined proxies for the children's physical fitness. To ensure that children really tried to reach their maximal physical capacity, their heart rate was observed with a Polar RS400 watch (Polar Electro Europe BV; Zug, Switzerland) and only results of children with more than 180 heart beats per min were considered valid. Throughout the shuttle run test, we monitored ambient air temperature and humidity, as these external factors might influence children's test performance.

8.3.2. Ethical approval

The study was approved by the institutional research commission of the Swiss Tropical and Public Health Institute (Basel, Switzerland) and received clearance from the ethics committees of Basel (EKBB, reference no. 377/09) and Côte d'Ivoire (reference no. 1993 MSHP/CNER). Insurance coverage was obtained from GNA Assurance (Abidjan, Côte d'Ivoire; policy no. 30105811010001).

At the end of the study, all children attending Grand Moutcho primary school were administered praziquantel (single 40 mg/kg oral dose) and albendazole (single 400 mg oral dose) free of charge, irrespective of their helminth infection status and whether or not they participated in the study. Children who required further medical treatment were referred to the local health service.

8.3.3. Data analysis

Data were double-entered and cross-checked in Access version 2007 (Microsoft Corporation; Redmond, WA, USA) and analysed in STATA version 10.1 (STATA Corporation; College Station, TX, USA). Questionnaire answers were coded as 1, 2 or 3 (for some questions also 4) with lower scores given to reports of more problems in a certain activity. The individual scores from questions 1 to 10 and 11 to 14, respectively (Appendix 13.4.1. Additional material. Questionnaire used to assess self-reported physical fitness in the present study; in French) were summed up in order to obtain a summary measure on PF (questions 1 to 10) and PR (questions 11 to 14). While PF is a summary measure for the ability to fulfill distinct physical tasks (e.g., walking, running and climbing), PR pertains to the physical potential to handle certain (social) roles (e.g., learning, helping and playing). According to this procedure, higher values for PF and PR indicate fewer problems in the respective domain. In a last step, scores for PF and PR were transformed to values between 0 and 100, according to equation (1):[25]

$$transformed\ score = \left[\frac{(actual\ raw\ score - lowest\ possible\ raw\ score)}{possible\ raw\ score\ range} \right] * 100 \qquad (1)$$

Helminth infection intensities were classified as light, moderate and heavy, using readily available guidelines from the World Health Organization (WHO).[26] Children's VO_2max was derived from equation (2), considering age (X_1 = age in years), the achieved maximal shuttle running speed (X_2 = speed in km/h) and a linear relation according to Léger and Mercier:[23]

$$VO_2 \max = 31.025 - 3.248 * X_1 + 3.238 * X_2 + 0.154 * X_1 * X_2 \qquad (2)$$

Two different samples were considered in the final analysis in order to assess also the value added by a QoL questionnaire. Sample 1 consisted of all children with complete questionnaire, parasitological and clinical data records. Sample 2 included all children from sample 1 who had not only complete questionnaire, parasitological and clinical data, but also valid physical fitness test results. An attrition analysis was carried out with those children who were included in sample 1, but not in sample 2, i.e., who had complete data records except for the physical fitness test. Besides descriptive statistics, Spearman rank correlation coefficient, uni- and multivariable linear regression models adjusted for participants' age and

sex, ambient air temperature and humidity, Fisher's test, χ^2 and t-test statistics were employed as appropriate to assess statistical significance ($p < 0.05$).

8.4. Results

8.4.1. Operational results

Operational results of the study are summarised in Figure 18. The two final study samples consisted of 167 children (97 boys and 70 girls) and 137 children (79 boys and 58 girls), both with a mean age of 12.0 years (range: 7-15 years). No statistically significant differences in terms of children's sex and age were identified between the two samples ($p > 0.05$). The 30 children (18 boys and 12 girls) who were part of sample 1 but excluded from sample 2 due to incomplete physical fitness test data had a mean age of 11.8 years (range: 8-14 years). Reasons for having no valid physical fitness test data were the exclusion from the shuttle run test due to medical concerns (i.e., dyspnea (n = 12), clinical malaria (n = 9), anemia (n = 2) and asthma (n = 1)) or reaching too low maximum heart rate (<180 beats per min) in the shuttle run test (n = 6).

8.4.2. Parasitological results

Tables 18 and 19 summarise the parasitological results. The prevalence of *S. haematobium*, *Plasmodium* spp., *S. mansoni*, hookworm and *A. lumbricoides* in the 167 children with complete parasitological results was 84.4%, 74.9%, 54.5%, 14.4% and 1.2%, respectively. No *T. trichiura* infection was diagnosed. High intensity helminth infections were common and only 10.8% of all children were completely helminth-free, while 32.9% harboured a single and 56.3% two or more helminth species concurrently. No significant differences in helminth prevalences, infection intensities or helminth co-infections were found between sample 1 and sample 2 ($p > 0.05$).

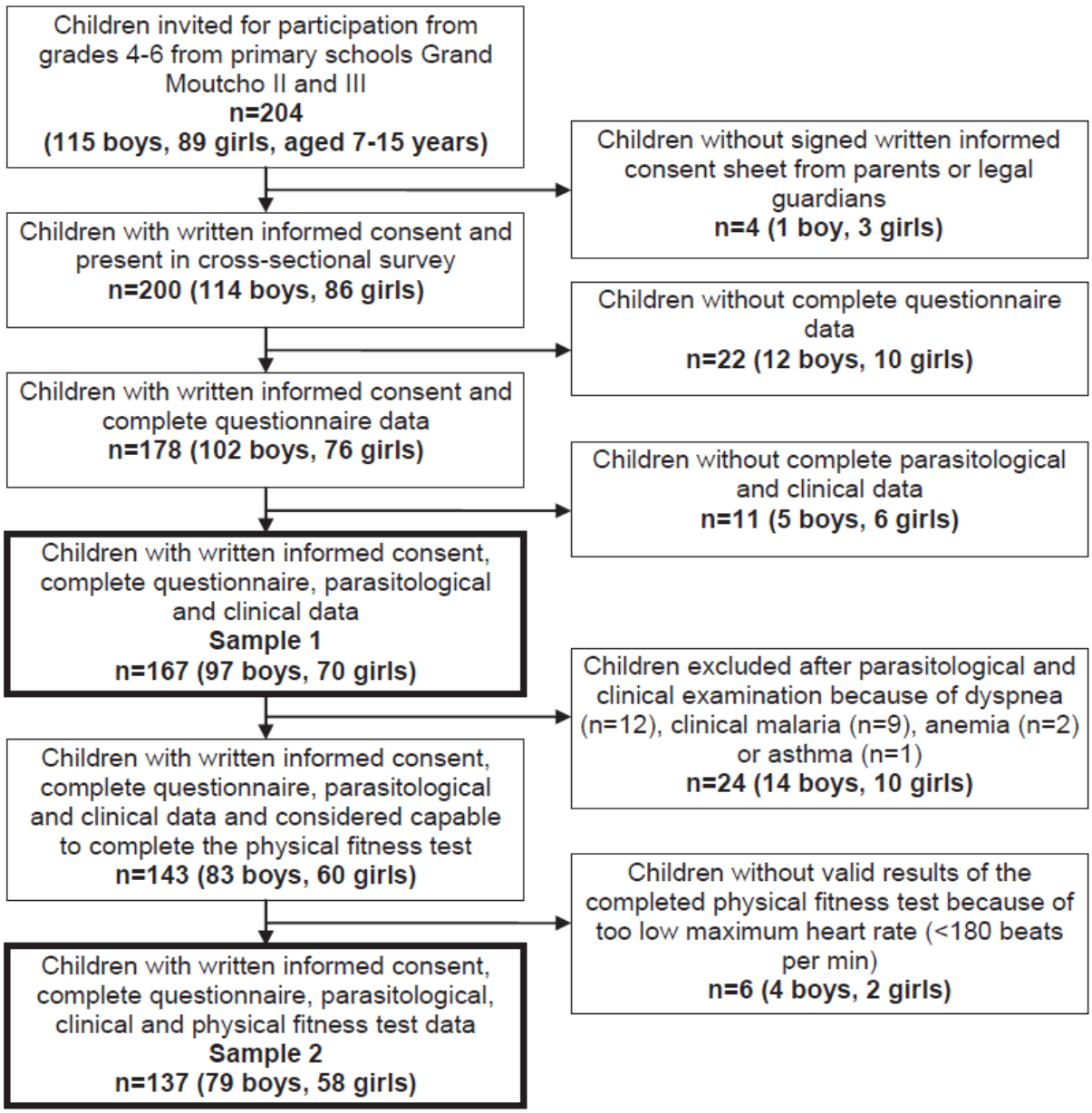

Figure 18. Flow chart detailing operational study results and the two different samples further considered in the analysis. The study was carried out in Grand Moutcho school, Agboville, Côte d'Ivoire, in early 2010.

Table 18. Parasitic infections and infection intensities in the two samples analysed.

Parasite	Infection	Sample 1			Sample 2		
		Male	Female	Total	Male	Female	Total
S. haematobium	no	18	8	26	14	7	21
	light (1-49 eggs/10 ml urine)	46	35	81	38	27	65
	heavy (≥50 eggs/10 ml urine)	33	27	60	27	24	51
S. mansoni	no	52	24	76	42	19	61
	light (1-99 EPG)	31	26	57	26	23	49
	moderate (100-399 EPG)	12	19	31	10	15	25
	heavy (≥400 EPG)	2	1	3	1	1	2
A. lumbricoides	no	96	69	165	78	57	135
	light (1-4,999 EPG)	1	0	1	1	0	1
	moderate (5,000-49,999 EPG)	0	1	1	0	1	1
Hookworm	no	78	65	143	64	53	117
	light (1-1,999 EPG)	18	5	23	15	5	20
	moderate (2,000-3,999 EPG)	1	0	1	0	0	0
Plasmodium spp.	no	24	18	42	23	15	38
	yes	73	52	125	56	43	99

Parasitological data stem from a study carried out in Grand Moutcho school, Agboville, Côte d'Ivoire, in early 2010.[17] Sample 1 with n = 167 observations (97 boys, 70 girls) includes all children with complete questionnaire, parasitological and clinical data. Sample 2 with n = 137 observations (79 boys, 58 girls) includes all children from sample 1 who had not only complete questionnaire, parasitological and clinical data, but also valid shuttle run test results (see also Figure 18). Infection intensities were defined according to WHO guidelines.[26] EPG = eggs per gram of stool.

Table 19. Helminth co-infections in the two samples analysed.

No. of concurrent helminth infections	Sample 1			Sample 2		
	Male	Female	Total	Male	Female	Total
Zero	13	5	18	11	4	15
One	35	20	55	27	16	43
Two	39	41	80	33	34	67
Three	9	4	13	7	4	11
Four	1	0	1	1	0	1

Parasitological data stem from a study carried out in Grand Moutcho school, Agboville, Côte d'Ivoire, in early 2010.[17] Sample 1 with n = 167 observations (97 boys, 70 girls) includes all children with complete questionnaire, parasitological and clinical data. Sample 2 with n = 137 observations (79 boys, 58 girls) includes all children from sample 1 who had not only complete questionnaire, parasitological and clinical data, but also valid shuttle run test results (see also Figure 18).

8.4.3. Results of the questionnaire survey and shuttle run test

Mean scores for PF were 51.3 (95% confidence interval (CI): 48.9-53.6) and 52.2 (95% CI: 49.8-54.7) in samples 1 and 2, respectively (Table 20). Mean scores for PR equalled 50.4 (95% CI: 46.7-54.0) and 51.3 (95% CI: 47.3-55.4). Means of the two objectively measured outcome variables, namely cumulative distance covered by the children in the shuttle run test and VO_2max, as measured only in sample 2, were 1,301 m (95% CI: 1,242-1,360 m) and 52.7 ml kg^{-1} min^{-1} (95% CI: 51.9-53.5 ml kg^{-1} min^{-1}), respectively.

Spearman rank correlation coefficients indicated statistically significant and positive correlation between PF and cumulative distance and VO_2max (Table 21). No such correlation was found between PR and the cumulative distance or VO_2max.

Uni- and multivariable regression models demonstrated statistically significant correlations of PF and sex with cumulative distance and of PF, sex and age with VO_2max (Table 22). PR showed no statistically significant association with the cumulative distance or VO_2max.

Despite diverse infection patterns of the children, uni- and multivariable regression models revealed no statistically significant correlations between participating schoolchildren's score on PF, which proofed to be valid as predictor for their physical fitness, and their parasitic infection status (Table 23).

Table 20. Summary of the questionnaire scores and shuttle run test results in the two samples analysed.

Test	Variable	Sample 1			Sample 2		
		Male	Female	Total	Male	Female	Total
Questionnaire score	Physical functioning	53.0	48.9	51.3	53.2	50.9	52.2
	Physical role	50.9	49.6	50.4	51.2	51.6	51.3
Shuttle run test	Distance	NA	NA	NA	1,452	1,094	1,301
	VO_2max	NA	NA	NA	54.5	50.3	52.7

Cumulative distance (in m) and VO_2max (in ml kg^{-1} min^{-1}) as objectively measured and questionnaire scores on physical functioning and physical role as self-reported variables in samples 1 and 2 from a study carried out in Grand Moutcho school, Agboville, Côte d'Ivoire, in early 2010.[17] Sample 1 with n = 167 observations (97 boys, 70 girls) includes all children with complete questionnaire, parasitological and clinical data. Sample 2 with n = 137 observations (79 boys, 58 girls) includes all children from sample 1 who had not only complete questionnaire, parasitological and clinical data, but also valid shuttle run test results (see also Figure 18). NA = not applicable.

Table 21. Spearman rank correlation coefficients.

	Distance		VO_2max	
	Coefficient	**p-value**	**Coefficient**	**p-value**
Physical functioning	0.215	0.012*	0.186	0.029*
Physical role	0.009	0.922	0.096	0.263

Cumulative distance (in m) and VO_2max (in ml kg^{-1} min^{-1}) as objectively measured and questionnaire scores on physical functioning (PF) and physical role (PR) as self-reported variables in sample 2 from a study carried out in Grand Moutcho school, Agboville, Côte d'Ivoire, in early 2010.[17] Sample 2 with n = 137 observations (79 boys, 58 girls) includes all children with complete questionnaire, parasitological, clinical and shuttle run test results (see also Figure 18). *Statistically significant ($p < 0.05$).

Table 22. Uni- and multivariable linear regression models.

Model	Explanatories	Distance			VO_2max		
		Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
Univariable	Physical functioning	5.13	1.12, 9.14	0.012*	0.07	0.01, 0.12	0.017*
	Physical role	0.50	-1.95, 2.96	0.685	-0.01	-0.05, 0.02	0.453
	Ambient air temperature	7.25	-11.17, 25.67	0.438	0.03	-0.22, 0.28	0.809
	Ambient air humidity	-2.44	-10.53, 5.66	0.553	0.01	-0.10, 0.12	0.888
	Sex	358.27	255.56, 460.98	< 0.001*	4.23	2.80, 5.66	< 0.001*
	Age	25.14	-8.29, 58.58	0.139	-1.13	-1.53, -0.72	< 0.001*
Multivariable[a,b]	Physical functioning	4.67	0.97, 8.36	0.014*	0.06	0.02, 0.11	0.008*
	Physical role	-0.61	-2.86, 1.63	0.589	-0.01	-0.04, 0.02	0.425
	Ambient air temperature	36.65	-7.34, 80.64	0.102	0.48	-0.06, 1.01	0.080
	Ambient air humidity	10.80	-8.61, 30.21	0.273	0.14	-0.10, 0.37	0.249
	Sex	359.28	257.96, 460.60	< 0.001*	4.36	3.13, 5.60	< 0.001*
	Age	23.51	-5.26, 52.29	0.108	-1.14	-1.49, -0.79	< 0.001*

Cumulative distance (in m) and VO_2max (in ml kg^{-1} min^{-1}) as objectively measured outcome variables and questionnaire scores on physical functioning and physical role as self-reported explanatories in sample 1 from a study carried out in Grand Moutcho school, Agboville, Côte d'Ivoire, in early 2010.[17] Sample 1 with n = 137 observations (79 boys, 58 girls) includes all children with complete questionnaire, parasitological, clinical and shuttle run test results (see also Figure 18). Ambient air temperature (in °C) and relative humidity (in %) as well as participants sex (reference: female) and age (in years) were included as potential confounders. CI = confidence interval. [a]Key indicators of the distance regression model: $F(6,130) = 10.53$, $p < 0.001$, $R^2 = 0.327$. [b]Key indicators of the VO_2max regression model: $F(6,130) = 17.26$, $p < 0.001$, $R^2 = 0.443$. *Statistically significant ($p < 0.05$).

Table 23. Uni- and multivariable linear regression models.

Model	Explanatories	Sample 1: Physical functioning		Sample 2: Physical functioning	
		Coeff. 95% CI	p-value	Coeff. 95% CI	p-value
Univariable	*S. haematobium* light infection	-4.01 -10.84, 2.83	0.249	-0.24 -7.46, 6.97	0.947
	S. haematobium heavy infection	-4.47 -11.59, 2.64	0.216	-1.39 -8.84, 6.07	0.713
	S. mansoni light infection	-3.22 -8.55, 2.10	0.234	-3.85 -9.33, 1.63	0.167
	S. mansoni moderate infection	-2.21 -8.69, 4.26	0.501	1.16 -5.63, 7.94	0.736
	S. mansoni heavy infection	3.97 -13.92, 21.85	0.662	-3.44 -23.98, 17.09	0.741
	A. lumbricoides light and moderate infection	3.79 -17.81, 25.38	0.730	2.81 -17.59, 23.22	0.785
	Hookworm light and moderate infection	3.15 -3.53, 9.84	0.353	2.08 -4.85, 9.00	0.554
	Concurrent helminth infections: one	-1.71 -9.95, 6.53	0.682	3.22 -5.33, 11.76	0.458
	Concurrent helminth infections: two	-4.73 -12.64, 3.19	0.240	-1.59 -9.73, 6.55	0.699
	Concurrent helminth infections: three and more	-0.95 -11.76, 9.86	0.862	3.75 -7.29, 14.79	0.503
	Plasmodium spp. Infection	-1.18 -6.60, 4.23	0.667	-1.83 -7.30, 3.62	0.507
	Sex	4.13 -0.59, 8.85	0.086	2.37 -2.57, 7.30	0.345
	Age	-0.13 -1.48, 1.22	0.849	-0.05 -1.44, 1.35	0.948

Table 23. Continued.

Model	Explanatories	Sample 1: Physical functioning			Sample 2: Physical functioning		
		Coeff.	95% CI	p-value	Coeff.	95% CI	p-value
Multivariable[a,b]	*S. haematobium* light infection	11.24	-34.86, 57.35	0.631	16.50	-27.75, 60.75	0.462
	S. haematobium heavy infection	10.88	-35.37, 57.13	0.643	15.96	-28.49, 60.40	0.479
	S. mansoni light infection	14.73	-30.72, 60.19	0.523	19.10	-24.10, 62.30	0.383
	S. mansoni moderate infection	17.47	-28.19, 63.14	0.451	25.80	-17.61, 69.21	0.242
	S. mansoni heavy infection	23.30	-25.63, 72.23	0.348	21.20	-26.58, 68.98	0.382
	A. lumbricoides light and moderate infection	12.51	-19.88, 44.91	0.447	11.80	-19.01, 42.61	0.450
	Hookworm light and moderate infection	17.82	-26.46, 62.09	0.428	20.03	-21.82, 61.89	0.345
	Concurrent helminth infections: one	-13.16	-59.73, 33.41	0.577	-13.10	-57.89, 31.70	0.564
	Concurrent helminth infections: two	-31.47	-122.23, 59.28	0.494	-38.70	-125.13, 47.73	0.377
	Concurrent helminth infections: three and more	-46.00	-180.52, 88.52	0.500	-53.39	-181.14, 74.37	0.410
	Plasmodium spp. Infection	-1.21	-6.94, 4.52	0.678	-2.05	-7.87, 3.76	0.486
	Sex	3.28	-1.82, 8.38	0.206	2.03	-3.25, 7.30	0.448
	Age	0.11	-1.38, 1.60	0.882	-0.01	-1.54, 1.53	0.992

Questionnaire scores on physical functioning as self-reported outcomes and helminth and *Plasmodium* spp. infections (reference: no infection) as parasitologically diagnosed explanatories in samples 1 and 2 from a study carried out in Grand Moutcho school, Agboville, Côte d'Ivoire, in early 2010.[17] Sample 1 with n = 167 observations (97 boys, 70 girls) includes all children with complete questionnaire, parasitological and clinical data. Sample 2 with n = 137 observations (79 boys, 58 girls) includes all children from sample 1 who had not only complete questionnaire, parasitological and clinical data, but also valid shuttle run test results (see also Figure 18). Infection intensities were defined according to WHO guidelines.[26] Categories of explanatories with $n \leq 1$ observations were combined with the next best category of the same explanatory. Participants sex (reference: female) and age (in years) were included as potential confounders. CI = confidence interval. [a]Key indicators of the regression model based on sample 1: $F(13,153) = 0.55$, $p = 0.891$, $R^2 = 0.045$. [b]Key indicators of the regression model based on sample 2: $F(13,123) = 0.66$, $p = 0.797$, $R^2 = 0.065$.

8.4.4. Results of the attrition analysis

An attrition analysis of the group of 30 children excluded in sample 2 showed that this group was neither significantly different in terms of their sex- or age-composition, nor their respective parasite prevalences, infection intensities or levels of multiple helminth species infections ($p > 0.05$). However, as expected because of their medical complaints, they reported lower PF scores as a group (mean = 46.8; 95% CI: 39.9-53.8). Furthermore, while the three completely parasite-free children achieved considerably higher mean PF scores (mean = 66.7; 95% CI: 16.5-116.9), the 27 parasitized children reported lower mean PF scores (mean = 44.6; 95% CI: 37.8-51.5) than their peers from sample 2 (Table 24).

Table 24. Attrition analysis of mean questionnaire scores on self-reported physical functioning.

Parasitic infection status	Sample 2			Excluded		
	n	Mean score PF	95% CI	n	Mean score PF	95% CI
Parasite-free	15	51.7	41.3, 62.1	3	66.7	16.5, 116.9
Parasitized	122	52.3	49.8, 54.8	27	44.6	37.8, 51.5
All	137	52.2	49.7, 54.7	30	46.8	39.9, 53.8

Questionnaire scores and parasitological results stem from a study carried out in Grand Moutcho school, Agboville, Côte d'Ivoire, in early 2010.[17] Sample 2 with n = 137 observations (79 boys, 58 girls) includes all children who had complete questionnaire, parasitological, clinical and also shuttle run test results (see also Figure 18). The group of excluded with n = 30 observations (18 boys, 12 girls) consists of all children with complete questionnaire, parasitological and clinical data, but no valid shuttle run test results. Together, the two groups add up to sample 1 with n = 167 observations (97 boys, 70 girls), which includes all children with complete questionnaire, parasitological and clinical data, but not necessarily valid shuttle run test results. PF = physical fitness. CI = confidence interval.

8.5. Discussion

To our knowledge, this is one of the first attempts to compare objectively measured and self-reported physical fitness in an area where malaria, schistosomiasis and soil-transmitted helminthiasis co-exist.[17] We found a significant association between the cumulative distance covered in a maximal multistage 20 m shuttle run test by 7-15 year old schoolchildren and the index PF, as calculated from children's answers to 10 questions in a simplified QoL questionnaire. The association between PF and the children's estimated VO_2max was also statistically significant, regardless of whether uni- or multivariable linear regression analyses were performed. VO_2max is a widely used proxy for the aerobe capacity, and hence a key

indicator for the physical performance of a person.[24] In contrast, the index PR, as calculated from the children's answers on four additional questions in the same simplified QoL questionnaire, was neither associated with cumulative distance nor VO_2max.

The findings that (i) PF was a better predictor than PR for objectively measured physical fitness in the present study and that (ii) the association between PF and cumulative distance was even better than the association between PF and VO_2max are reasonable. These claims are justified as follows. First, PF literally includes questions about fulfilling distinct physical functions such as running (questions 1 and 2), climbing a hill (questions 4 and 5) or walking (questions 7 to 9), while PR is more concerned with the physical ability to fulfil certain (social) roles (questions 11 to 14). Second, three questions (questions 7 to 9) are directly asking about the ability to cover certain distances (Appendix 13.4.1. Additional material. Questionnaire used to assess self-reported physical fitness in the present study; in French).

Interestingly, no association between parasitic infection status and the indices based on self-reported physical fitness was identified. However, by logical deduction, this finding had to be expected after no association was detected between parasitic infections and the objectively measured physical fitness in the umbrella study into which the current investigation was embedded[17] and a strong association was found between the objectively measured physical fitness and self-reported physical fitness in the present study. The finding that the parasitic infection status does not prejudice physical fitness is also in line with some older investigations,[27,28] but contradicts newer research[29-31] and the widely held belief that schistosmiasis, soil-transmitted helminthiasis and malaria impair the infected individuals' physical fitness. Some potential explanations and approaches for further research to better understand and solve this discrepancy have been discussed elsewhere.[17] In brief, the participating Ivorian schoolchildren presented with clearly better physical fitness as for example age-matched Canadian counterparts.[23] Differences in life-styles and nutrition might, at least to some degree, explain this observation.[32-35] It has also been implied that the Ivorian children with a parasitic infection could maybe mask the incurred disability by their generally excellent level of physical fitness. The children may adapt quite well to parasitic infections that are acquired early in their life and the children do not yet experience disability caused by advanced chronic disease. Furthermore, it has been suggested that children attending school might not be fully representative in a given epidemiological setting, as children from poorest and furthest away households are less likely to be registered at school and at the same time more likely to be infected with parasites. It is also conceivable that children really suffering

from the adverse effects of the infections rest at home because of their signs and symptoms, and hence did not take part in our study.

Of particular interest was the fact that the use of a QoL questionnaire, which proofed to be a valid tool to assess the schoolchildren's physical fitness in the respective study area, permitted the inclusion of an additional 30 children who had to be excluded from the shuttle run test due to medical concerns. An attrition analysis indicated that this excluded group of children was not different from the group that could successfully complete the shuttle run test with regard to sex, age or parasitic infection status. However, the mean PF scores of the parasitized and excluded children was considerably lower than the mean PF scores of the children who were parasitized as well but able to participate in the shuttle run test. It could be hypothesized that mainly children who suffer the most from their parasitic infections were excluded from the physical fitness test – precisely because of experiencing severe sequelae. Supposedly due to the relatively small sample size, which was at least partially owed to our rigorous study design, the difference in PF between the two groups showed no statistical significance. As revealed by the analysis of the two different samples in Table 8.6., the inclusion of the 30 children who were probably most seriously affected by parasitic infections could not overpower the results of the other 137 children. Nevertheless, their inclusion was only possibly thanks to the QoL questionnaire results and their exclusion would have led most likely to biased results.

8.6. Conclusion

We consider the questionnaire employed in the present study as a valid tool to assess schoolchildren's physical fitness in the respective study area. Nevertheless, further validation in other settings of Côte d'Ivoire (e.g., urban areas) and elsewhere in sub-Saharan Africa is warranted. The questionnaire was particularly useful in assessing physical fitness of those children who were unable to complete an exhausting physical fitness test. Future and preferably larger studies to assess disability caused by helminthic infections, other NTDs and malaria should use a test-retest design with intermittent treatment or even piggyback on continuous preventive chemotherapy campaigns. Furthermore, they should also consider dimensions of QoL other than physical fitness, for instance bodily pain and potentially following affection of vitality, mental health and social functioning. However, these dimensions are exceedingly difficult to measure with tools that do not include one or the other form of a questionnaire. This is even more true when affection is subtle as it is often the case

with NTDs. We believe that QoL questionnaires will gain further importance in eliciting and quantifying disability caused by NTDs. Hence, further development and validation of such tools, for instance by using mixed methods triangulation approaches, is warranted.

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9. Schistosomiasis, soil-transmitted helminthiasis, and socio-demographic factors influence quality of life of adults in Côte d'Ivoire

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9.1. Abstract

Background: Burden of disease estimates are widely used for priority setting in public health and disability-adjusted life years are a powerful ‘‘currency’’ nowadays. However, disability weights, which capture the disability incurred by a typical patient of a certain condition, are fundamental to such burden calculation and their determination remains a widely debated issue.

Methodology: A cross-sectional epidemiological survey was conducted in the recently established Taabo health demographic surveillance system (HDSS) in south-central Côte d’Ivoire, to provide new, population-based evidence on the disability caused by schistosomiasis and soil-transmitted helminthiasis. Parasitological results from stool, urine, and blood examinations were juxtaposed to quality of life (QoL) questionnaire results from 187 adults. A multivariable linear regression model with stepwise backward elimination was used to identify significant associations, considering also socio-demographic characteristics obtained from the Taabo HDSS database.

Principal findings: Prevalences for hookworm, *Plasmodium* spp., *Trichuris trichiura*, *Schistosoma haematobium* and *Schistosoma mansoni* were 39.0%, 18.2%, 2.7%, 2.1% and 2.1%, respectively. *S. mansoni* and *T. trichiura* infections of any intensity reduced the participants’ self-rated QoL by 16 points (95% confidence interval (CI): 4-29 points) and 13 points (95% CI: 1-24 points), respectively, on a scale from 0 (worst QoL) to 100 points (best QoL). The only other statistically significant effect was a 1-point (95% CI: 0.1-2 points) increase on the QoL scale per one unit increase in a calculated wealth index.

Conclusions/Significance: We found consistent and significant results on the negative effects of schistosomiasis and soil-transmitted helminthiasis on adults’ self-rated QoL, also when taking socio-demographic characteristics into account. Our results warrant further investigation on the disability incurred by helminthic infections and the usefulness of generic QoL questionnaires in this endeavor.

Keywords: Schistosomiasis, soil-transmitted helminthiasis, *Plasmodium* spp., quality of life, questionnaire, Côte d’Ivoire.

9.2. Author summary

In public health, ‘‘burden’’ estimates should capture the human suffering caused by certain health states, and the estimates are often used for priority setting. However, such ‘‘burden’’ estimates need to assess not only the number of affected people by certain conditions, but also the disability incurred by the average patient, and the determination of the degree of disability remains a widely debated issue. In order to provide new, population-based evidence on the disability caused by infections with parasitic worms, we administered a quality of life (QoL) questionnaire to 187 adults in rural Côte d'Ivoire and concurrently examined them for parasitic worm infections. We also considered socio-demographic characteristics in our analysis. In comparison with their non-infected counterparts, infected people reported a 13-16 points lower QoL on a scale from 0 (worst QoL) to 100 points (best QoL). At the same time, a one unit increase in a calculated wealth index revealed a 1-point increase in the participants' QoL. The results are consistent and warrant further investigation on the disability induced by parasitic worm infections and the usefulness of QoL questionnaires in this endeavor.

9.3. Introduction

Efforts are underway for a comprehensive revision of the global burden due to major diseases, injuries, and risk factors.[1] The initial global burden of diseases, injuries, and risk factors study, commissioned by the World Bank more than 20 years ago, introduced the disability-adjusted life year (DALY) metrics.[2] DALY is a time-based measure, which combines years of life lost (YLL) due to premature death, and years of life lived with disability (YLD) due to a certain condition.[2] Results from the initial global burden of disease study have been widely used for priority setting in research, policy, and practice, and the DALY became a powerful ‘‘currency’’ in public health (see for example reference [3]).

An undeniable merit of the global burden of disease concept is the renewed interest in descriptive epidemiology and population health measurement. Not surprisingly though, the concept also stimulated considerable controversies. Amongst other issues, criticism about the disability weights, which should measure the disability caused by a certain condition on a continuous scale from 0 (perfect health) to 1 (death), was raised as the original disability weights were solely based on expert opinion.[2,4,5] In order to respond to such shortcomings, the disability weights will be adapted in the current revisions of the global burden of diseases, injuries, and risk factors. According to the operations manual on the project’s homepage,[6] the revised disability weights will be elicited not only by expert opinion, but also by an Internetsupported, multi-method study among qualified respondents and, for selected sequelae, by population-based discrete choice assessments.

In order to provide new, setting-specific, population-based evidence on the disability caused by schistosomiasis and soil-transmitted helminth infections, we conducted a cross-sectional survey among adults in the Taabo health demographic surveillance system (HDSS), in south-central Côte d’Ivoire. Generic quality of life (QoL) questionnaires and standardized, qualitycontrolled parasitological methods were applied and the results juxtaposed, taking into consideration readily available socio-demographic data from the Taabo HDSS database as potential confounders. To our knowledge, only few studies employed generic QoL questionnaires to assess disability attributable to helminth infections.[7-10] However, these studies focused on school-aged children[8,9] and other narrowly defined population subgroups (e.g., patients with advanced, chronic infections).[7,10] The present study provides new insight regarding the usefulness and applicability of generic QoL questionnaires to elicit disabilities due to helminthiases in the general public.

9.4. Materials and methods

9.4.1. Ethics statement

The study protocol was approved by the institutional research commissions of the Swiss Tropical and Public Health Institute (Swiss TPH; Basel, Switzerland) and the Centre Suisse de Recherches Scientifiques en Côte d'Ivoire (CSRS; Abidjan, Côte d'Ivoire). Ethical clearance was provided by the ethics committee of Basel (EKBB; reference no. 316/08) and the Comité National d'Ethique et de la Recherche (CNER) in Côte d'Ivoire (reference no. 1086 MSHP/CNER).

The Taabo HDSS was set-up in mid-2008, located in the Taabo area in the south-central part of Côte d'Ivoire. While establishing the Taabo HDSS, district and village authorities and the general public were informed about its purpose, operational procedures, potential risks, and benefits. The present study was carried out in June 2010, readily embedded in the second crosssectional epidemiological survey pursued once every year. Written informed consent was obtained from all participants. It was emphasized that participation was voluntary, and hence people could withdraw anytime without further obligation. All results were coded and kept confidential. At the end of the study, all people living in the Taabo HDSS were invited for deworming with albendazole (400 mg single oral dose) and ivermectin (~200 μg/kg using a dose pole) irrespective of participants' infection status.[11,12] Additionally, a physician was present during our study and treated acute cases of infections, other diseases and injuries, or referred people to the district hospital in Taabo Cité if need be. Preventive chemotherapy against schistosomiasis, using praziquantel (~40 mg/kg according to a dose pole), was administered 6 months later.

9.4.2. Study area and population

The Taabo HDSS covers most of the rural Sous-Préfecture Taabo. Its main office is located in Taabo Cité, 160 km north-west of Abidjan. The region's tropical climate follows a seasonal pattern with a long dry season between November and April and two rainy seasons, a long one between April and July and a shorter one in September and October.[13,14] The area is at the interface of tropical rainforest in the south and the savannah in the north with the Bandama River running through from north to south. In 1979, construction of a large hydroelectric dam was completed (Figure 19).[15] Malaria[16] and neglected tropical diseases (e.g.,

schistosomiasis[13,15,17] and soil-transmitted helminthiasis[13,18]) are endemic and rapid re-infection of *Schistosoma haematobium* has been observed after praziquantel administration.[17]

Vital statistics (i.e., pregnancy, birth, death, in-migration, and out-migration) and the health of some 38,500 individuals registered in the Taabo HDSS are monitored longitudinally. People are mainly engaged in subsistence farming of manioc, yams, and banana, while cacao and coffee are farmed as cash crops.[13,14] There are also some fishermen around Lake Taabo, some artisans, and – particularly in Taabo Cité – some shopkeepers and businessmen.

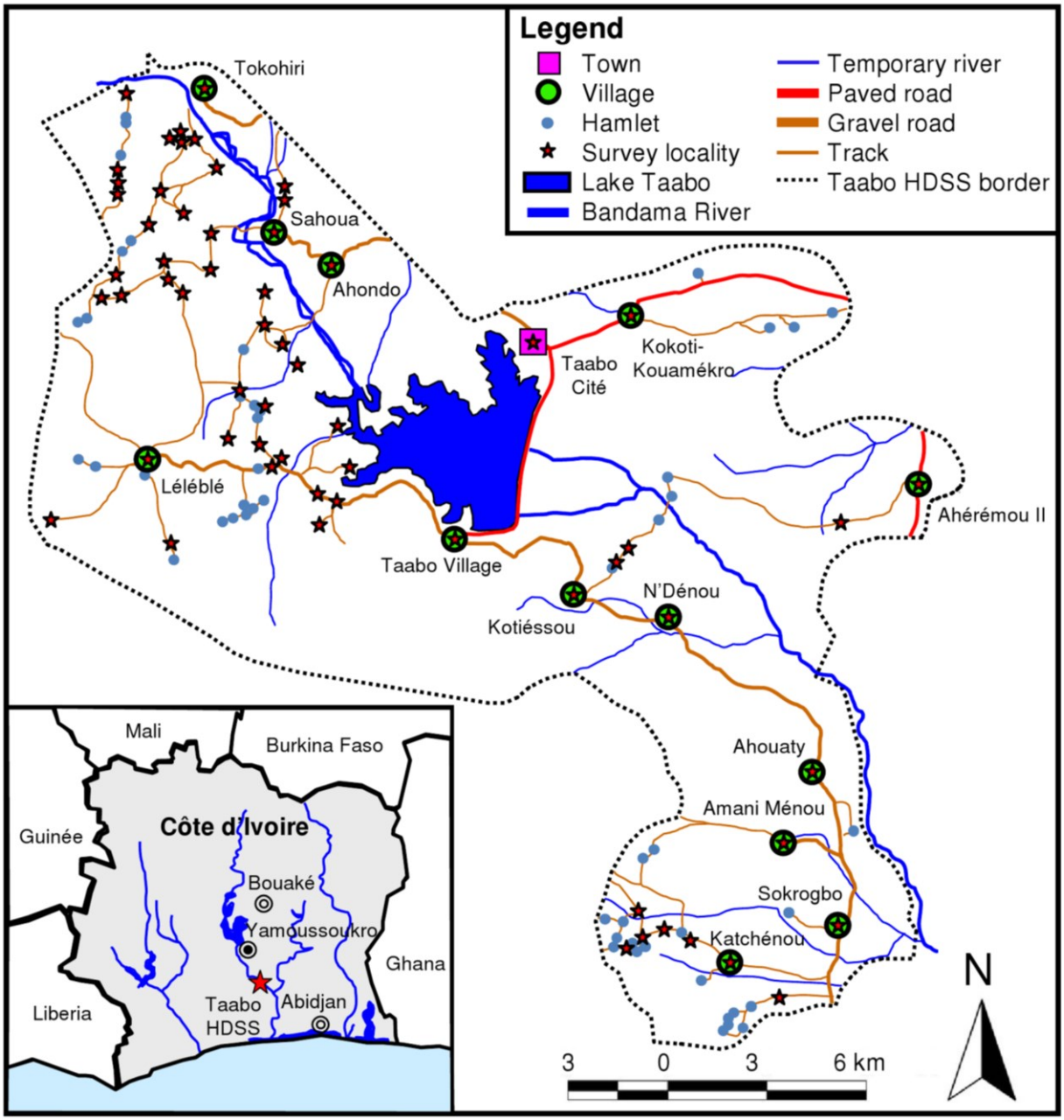

Figure 19. Map of the Taabo health demographic surveillance system (HDSS) and predefined survey locations. The study was carried out in June 2010, readily embedded in the second annual cross-sectional epidemiological survey of the Taabo HDSS.

9.4.3. Individual and household data compilation

For the present study, socio-demographic data on individual and household level were obtained from the Taabo HDSS database. Individual data included sex, age, relationship with the head of household, education, and main occupation. Household-level data contained information on the households' location, the number of household members, housing construction material, availability of certain facilities, and the possession of equipment.

9.4.4. Field and laboratory procedures

All collaborators, including local health personnel, were trained and informed about the purpose, procedures, potential risks, and benefits of the cross-sectional survey and the deworming. Subsequently, key informants, field enumerators, and supervisors of the Taabo HDSS and the local health personnel informed all heads of households to visit, together with their families, a predefined, nearby survey location on a specified date and time to receive anthelmintic treatment. In addition, approximately 7% of all households in the Taabo HDSS were selected by stratified random sampling. These households were visited the day before the treatment and two plastic containers were distributed to all household members for collection of a lemon-sized fresh morning stool and a urine sample the next day.

On the day of treatment, people not selected for in-depth clinical and parasitological examinations received albendazole and ivermectin and they could continue with their daily chores (Figure 20). People who suffered clinical episodes (e.g., infants with an axillary temperature ≥37.5°C and a history of fever) were seen by a physician and provided antimalarial treatment or other specific interventions if need be. Families selected for clinical and parasitological examinations were sent to a first post to provide written informed consent and collection of stool and urine samples. At a second post, qualified technicians measured participants' weight and height and took a finger prick blood sample. One drop of blood was taken for a rapid diagnostic test (RDT) for malaria (ICT ML01 malaria Pf kit, ICT Diagnostics; Cape Town, South Africa), another drop for the analysis of hemoglobin (HemoCue Hb 301 System, HemoCue; Ängelholm, Sweden), and another two drops for thin and thick blood film preparation on microscope slides. At post three, trained field enumerators invited the heads of households and, if possible, a second adult household member of the opposite sex to independently fill out a questionnaire. At the next post, participants were clinically examined by a physician and, if need be, given specific treatment according to

national guidelines. In a last step, participants were sent to the albendazole and ivermectin treatment post.

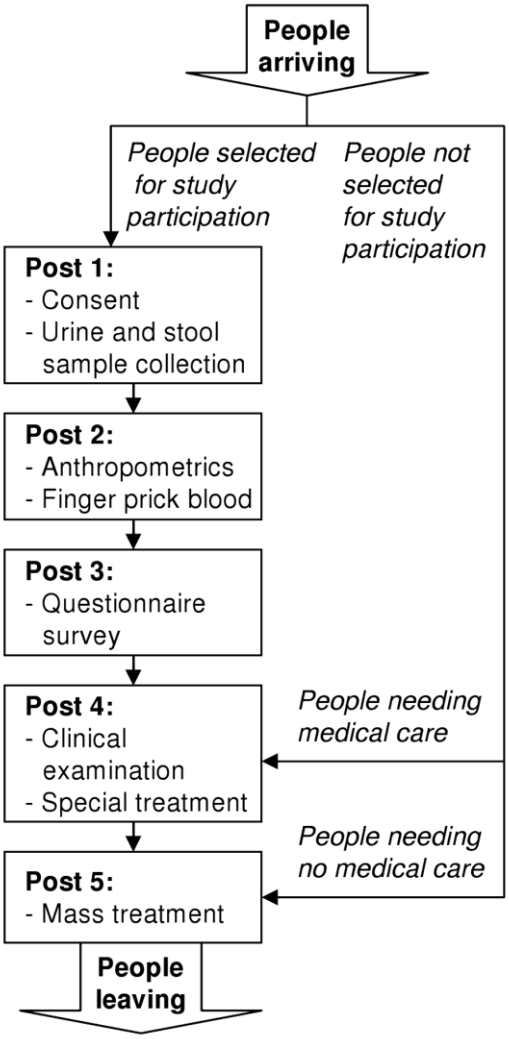

Figure 20. Flow chart of the study procedure in the field. The study was carried out in June 2010, readily embedded in the second annual cross-sectional epidemiological survey of the Taabo health demographic surveillance system (HDSS). In the frame of this second annual cross-sectional epidemiological survey, the whole population of the Taabo HDSS was offered anthelmintic treatment with albendazole and ivermectin. At the same time, people selected for an in-depth clinical and parasitological examination were invited to visit a series of different posts, including a quality of life (QoL) questionnaire for heads of households and a second adult household member of the opposing sex.

Blood, stool, and urine samples were transferred to the laboratory of the hospital in Taabo Cité and worked up the same day using standardized, quality-controlled techniques as described elsewhere.[13,14,19-21] In short, duplicate 41.7 mg Kato-Katz thick smears were prepared from each stool sample. After a clearing time of 30-45 min, the thick smears were

examined under a microscope for soil-transmitted helminths (*Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm) and *Schistosoma mansoni*. The sum of the helminth-specific egg counts of the two Kato-Katz thick smears were multiplied by a factor 12 to obtain infection intensities, as expressed in eggs per gram of stool (EPG). Urine samples were vigorously shaken, 10 ml drawn up into a syringe and pressed through a meshed nylon filter with a pore size of 20 mm (Sefar AG; Heiden, Switzerland). Next, filters were placed on a microscope slide and, after adding a drop of Lugol, examined for *S. haematobium* eggs under a light microscope. All parasitological examinations were performed by experienced laboratory technicians. For quality control, ~5% of all microscope slides were re-examined by a senior technician. In case of disagreement, slides were read a third time and the result discussed among the technicians until agreement was reached. Thin and thick blood films were stained with Giemsa and examined for *Plasmodium* parasitemia.

9.4.5. Questionnaire survey

We used previously employed questionnaires in Côte d'Ivoire[22-25] and developed them further so that they allowed us to assess risk factors, signs, and symptoms related to neglected tropical diseases and malaria, and added one section pertaining to the respondent's QoL. The World Health Organization (WHO) Quality of Life-BREF (WHOQOL-BREF) questionnaire[26] served as template for the section on QoL, as previous studies with other generic questionnaire tools revealed ambiguous results in the People's Republic of China[7,8,10] and also in a first pre-testing in the frame of another study in the Taabo HDSS[13] (data on pre-testing of QoL questionnaires not shown).

The initial version of the questionnaire after translation into French was discussed with the field enumerators and supervisors of the Taabo HDSS. These field enumerators and supervisors are locals, who live in the different communities of the Taabo HDSS, are able to read, write, and speak French as well as the local languages Baoulé, Dioula, or Senufo. The questionnaire was further adapted based on their comments, then pre-tested in a nearby village and again refined in order to obtain the finally applied version (Appendix 13.5.2. and 13.5.3.). During the survey, the same field enumerators and supervisors of the Taabo HDSS conducted the interviews, either in French or any of the aforementioned local languages.

9.4.6. Statistical analysis

Data were double-entered and cross-checked in EpiInfo version 3.5.1 (Centers for Disease Control and Prevention; Atlanta, United States of America) and analyzed in STATA version 10.1 (STATA Corp.; College Station, United States of America). For convenience, the myriad of main occupations obtained from the Taabo HDSS database were categorized into primary economic sector (i.e., making direct use of natural resources, such as farming), secondary economic sector (i.e., producing manufactured and other processed goods), and tertiary economic sector (i.e., producing services, such as education and health care), with housewives included in the primary sector as they are usually involved in (subsistence) farming. Socio-economic household data were used to calculate an assetbased wealth index and deduce the inhabitants' socio-economic status, according to an approach put forth in a World Bank publication.[27] The results on soil-transmitted helminth infections and schistosomiasis were classified into infection intensities (light, moderate, and heavy) according to WHO guidelines.[11] Malaria results from RDTs could only be considered as binary variables (positive/negative). Information on QoL was analyzed and summarized according to the WHOQOL user manual.[28] Questionnaire answers on QoL were coded as 1, 2, 3, or 4 with higher scores indicating elevated QoL (Appendix 13.5.2. and 13.5.3.). The individual scores from questions 11, 12, 16, 17, 18, and 24 were summed up to form the score on domain 1 about the environmental well-being; the individual scores from questions 19, 21, 22, 23, and 25 were added and formed the score on domain 2 about the psychological well-being; the individual scores from questions 10, 13, 20, 26, 27, 28, and 29 were summed up to form the score on domain 3 about the physical well-being; and the individual scores from questions 14 and 15 were added and formed the score on domain 4 about the social well-being. All individual scores from questions 9 to 29 were summed up to form each participant's overall score on QoL. All scores were transformed to values between 0 and 100 (i.e., percentages) according to equation (1):

$$transformed\ score = \left[\frac{(actual\ raw\ score - lowest\ possible\ raw\ score)}{possible\ raw\ score\ range} \right] * 100 \qquad (1)$$

A Kruskal-Wallis test was performed to check for statistically significant ($p < 0.05$) variations in the mean QoL scores assessed by the different interviewers (i.e., check for inter-

observer variation). Furthermore, to assess the internal consistency and validity of the resulting QoL scores, we used Cronbach's alpha and a univariable linear regression model with the calculated overall QoL scores as outcome and the QoL ratings directly expressed by the participants in the final question of the questionnaire as explanatory variable (Appendix 13.5.2. and 13.5.3., see question 30: ''How would you rate your quality of life in general? Very good? Good? Bad? Very bad?'').

Wilcoxon rank sum and Kruskal-Wallis test, χ^2 and Fisher's exact test were employed, as appropriate, to check for statistically significant univariable associations between the different socio-demographic, parasitological, and Qol indicators. The outcome on QoL was further scrutinized in a multivariable linear regression analysis with socio-demographic data (i.e., age, sex, education, occupation, and socio-economic status) and parasitological findings (i.e., schistosomiasis, soil-transmitted helminth infections, and malaria) as explanatory variables, considering also potential clustering of the results in interviewers and residential areas. A stepwise backward elimination procedure of non-significant explanatory factors was adopted to identify those variables most significantly influencing the participants' scores on QoL. In each iteration, the explanatory variable with the highest p-value was eliminated as long as the Akaike information criterion (AIC) was decreasing and the likelihood ratio test indicated no statistically significant association between the eliminated explanatory variable and the QoL scores. Categories of the same explanatory variable were combined, based on expert knowledge and logical deduction, before eventually eliminating the respective variable.

Only participants with signed written informed consent and complete data records (i.e., responses to all questions, duplicate Kato-Katz thick smears, urine filtration, and RDT for malaria) were included in the final analysis. Participants with completed written informed consent and questionnaire, but incomplete parasitological results were included in an attrition analysis.

9.5. Results

9.5.1. Operational results and socio-demographic characteristics

Overall, 255 adults were invited to participate in the study (Figure 21). Seven did not provide written informed consent or were unwilling to participate in the questionnaire survey, mostly because they were pressed for time. Moreover, 36 adults had no valid results from stool examination, as they failed to provide sufficiently large stool samples for duplicate Kato-Katz

thick smear examination. Another 17 individuals had no valid results from the urine examination and eight were excluded as they did not have any malaria RDT results. Hence, the final study sample consisted of 187 adults; 98 males and 89 females. The median age was 45 years for both males (range: 18-87 years) and females (range: 21-83 years) (p = 0.926). About half (n = 92, 49.2%) of the participants were heads of household.

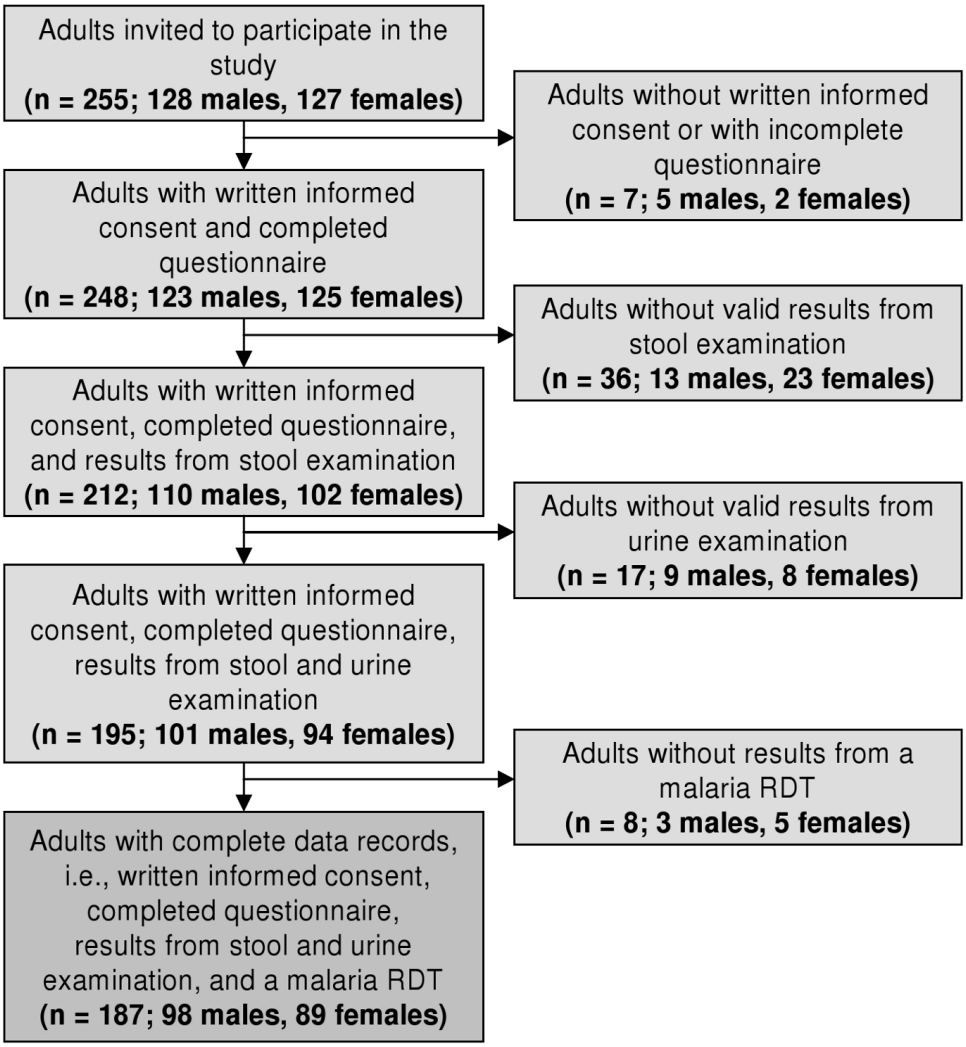

Figure 21. Flow chart of the participation and compliance in the present study. The study was carried out in June 2010, readily embedded in the second annual cross-sectional epidemiological survey of the Taabo health demographic surveillance system.

The educational level and the main sector of occupation are summarized in Table 25. The data on education reveal that a substantial number of participants have never attended school and, whereas the differences between age groups were not statistically significant ($p = 0.663$), women reported a significantly lower educational level than men ($p = 0.046$). Differences in occupational sector categorization showed no statistically significant difference between sex ($p = 0.295$) and age groups ($p = 0.218$) with most participants working in the primary sector (mainly subsistence farming) and only very few in the secondary sector. Not surprisingly, higher educated people were more often working in the tertiary rather than in the primary or secondary sectors ($p < 0.001$).

Results from the socio-economic analysis are shown in Table 26. According to the wealth quintiles, participants' socio-economic status were not significantly related to sex ($p = 0.377$) or age group ($p = 0.060$), but positively associated with the educational level and working in the tertiary sector (both $p < 0.001$).

Table 25. Educational level and main sector of occupation among 187 adults in rural Côte d'Ivoire.

Age (years)	Sex	Number asked	Educational level				Main sector of occupation		
			None	Primary school	Secondary school	Higher education	Primary[a]	Secondary[b]	Tertiary[c]
18-40	Male	37	15	11	9	2	31	1	5
	Female	29	19	5	4	1	23	0	6
41-60	Male	36	12	10	13	1	26	1	9
	Female	48	30	8	8	2	29	4	15
60+	Male	25	17	1	7	0	19	1	5
	Female	12	7	4	1	0	8	1	3
All	Male	98	44	22	29	3	76	3	19
All	Female	89	56	17	13	3	60	5	24
All	Both	187	100	39	42	6	136	8	43

Educational level and main sector of occupation among 187 adults interviewed in the Taabo health demographic surveillance system, south-central Côte d'Ivoire, in June 2010. Results are stratified by age and sex. [a]Participants being farmer, fisher, hunter, or housewife. [b]Participants being builder or artisan. [c]Participants being driver, housekeeper, watchman, merchant, trader, hairdresser, gastronome, healer, nurse, teacher, student, office worker, or policeman.

Table 26. Overview of asset possession and the calculated socio-economic status among 187 adults in rural Côte d'Ivoire.

Asset	Percentage of participants possessing the asset					
	Total	Wealth quintiles				
		Most poor (n = 39)	Very poor (n = 36)	Poor (n = 38)	Less poor (n = 37)	Least poor (n = 37)
Type of housing						
Traditional hut	31.0	66.7	63.9	18.4	5.4	0.0
Barrack	1.1	5.1	0.0	0.0	0.0	0.0
Collective dwelling	1.1	0.0	0.0	0.0	2.7	2.7
Simple house	7.0	0.0	0.0	2.6	8.1	24.3
Row house	18.7	0.0	2.8	5.3	40.5	46.0
Modern house	22.5	0.0	11.1	42.1	32.4	27.0
Other housing	18.7	28.2	22.2	31.6	10.8	0.0
People per sleeping room[a]	2.1	2.3	1.9	1.8	2.5	2.2
Main lighting at home						
Lantern	29.4	87.2	58.3	0.0	0.0	0.0
Fix electric lighting	65.8	0.0	30.6	100.0	100.0	100.0
Other lighting	4.8	12.8	11.1	0.0	0.0	0.0
Energy source for cooking						
Wood	80.8	100.0	94.4	100.0	81.1	27.0
Wood + coal	10.7	0.0	0.0	0.0	13.5	40.5
Coal	3.7	0.0	0.0	0.0	5.4	13.5
Gas + coal	1.6	0.0	5.6	0.0	0.0	2.7
Gas	3.2	0.0	0.0	0.0	0.0	16.2
Equipment						
Hand barrow	9.6	0.0	11.1	5.3	13.5	18.9
Cistern	32.6	30.8	22.2	50.0	29.7	29.7
Mobile phone	67.4	20.5	80.6	65.8	78.4	94.6
Radio	64.2	46.2	69.4	55.3	64.9	86.5
TV	33.2	0.0	0.0	23.7	54.1	89.2
Pirogue	6.4	2.6	8.3	10.5	8.1	2.7
Bicycle	73.8	76.9	72.2	79.0	73.0	67.6
Moped	13.9	0.0	0.0	13.2	13.5	43.2
Ventilator	27.8	0.0	0.0	13.2	46.0	81.1
Fridge	5.9	0.0	0.0	0.0	2.7	27.0
Freezer	5.9	0.0	0.0	0.0	0.0	29.7

Overview of asset possession and the calculated socio-economic status among 187 adults interviewed in the Taabo health demographic surveillance system, south-central Côte d'Ivoire, in June 2010. [a]Reports the average number of people per sleeping room in the respective wealth quintile.

9.5.2. Parasitological results

Sex- and age-specific prevalence and intensity of helminth infection and *Plasmodium* infection are summarized in Table 27. We found hookworm, *Plasmodium* spp., *T. trichiura*, *S. haematobium* and *S. mansoni* prevalences of 39.0%, 18.2%, 2.7%, 2.1% and 2.1%, respectively. Most helminth infections were of light intensity and no heavy infections were diagnosed at all. With the exception of a higher prevalence of *Plasmodium* spp. infection in people aged 60 years and above ($p = 0.028$), no significant differences occurred in the prevalence and intensity of helminth and *Plasmodium* infection with regard to sex, age group, educational level, and occupational sector. Regarding participants' socio-economic status, hookworm prevalence ($p < 0.001$) and infection intensity ($p = 0.002$) as well as *T. trichiura* prevalence ($p = 0.025$) were significantly lower in wealthier participants.

9.5.3. Self-reported QoL

Thirteen different field enumerators and supervisors of the Taabo HDSS were involved in interviewing the study participants, with no statistically significant inter-observer variation in reported mean QoL scores ($p = 0.104$). The mean summary score on QoL was 63.9 (range: 21.2-93.9) and Cronbach's alpha (0.805) indicated a good internal consistency of the QoL scores. The univariable linear regression model with the calculated QoL summary scores as outcome, and the QoL ratings directly expressed by the participants as explanatory variable, indicated a statistically significant positive correlation ($p < 0.001$). The calculated scores on the four different domains and the summary score on QoL are illustrated in Figure 22. Generally lower scores were obtained for the domains comprising the participants' environment and psychological well-being, and higher scores for the physical and social well-being.

The mean domain and overall QoL scores in relation to socio-demographic and parasitological variables are shown in Table 28. The only statistically significant differences in the univariable analysis were an increased score in the environmental well-being of higher educated people ($p = 0.043$), those belonging to the wealthiest quintile ($p = 0.006$), and people with no hookworm infection ($p = 0.002$).

Table 27. Prevalence and intensities of helminth and *Plasmodium* spp. infections, stratified by age and sex among 187 adults in rural Côte d'Ivoire.

Parasitic infection (in %)		18-40 years old		41-60 years old		60+ years old		All ages		
		Male (n = 37)	Female (n = 29)	Male (n = 36)	Female (n = 48)	Male (n = 25)	Female (n = 12)	Male (n = 98)	Female (n = 89)	Both sexes (n = 187)
S. haematobium [a]	Negative	100.0	100.0	100.0	93.7	96.0	100.0	99.0	96.6	97.9
	Light	0.0	0.0	0.0	6.3	4.0	0.0	1.0	3.4	2.1
	Heavy	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S. mansoni [b]	Negative	97.3	100.0	100.0	93.7	100.0	100.0	99.0	96.6	97.9
	Light	2.7	0.0	0.0	4.2	0.0	0.0	1.0	2.3	1.6
	Moderate	0.0	0.0	0.0	2.1	0.0	0.0	0.0	1.1	0.5
	Heavy	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Hookworm [b]	Negative	56.8	62.1	63.9	64.6	52.0	66.7	58.1	64.0	61.0
	Light	43.2	37.9	33.3	35.4	40.0	33.3	38.8	36.0	37.4
	Moderate	0.0	0.0	2.8	0.0	8.0	0.0	3.1	0.0	1.6
	Heavy	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
A. lumbricoides [b]	Negative	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
	Light	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Moderate	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Heavy	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
T. trichiura [b]	Negative	94.6	96.5	100.0	100.0	96.0	91.7	96.9	97.8	97.3
	Light	5.4	3.5	0.0	0.0	4.0	0.0	3.1	1.1	2.2
	Moderate	0.0	0.0	0.0	0.0	0.0	8.3	0.0	1.1	0.5
	Heavy	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Plasmodium spp. [c]	Negative	78.4	79.3	88.9	89.6	68.0	75.0	79.6	84.3	81.8
	Positive	21.6	20.7	11.1	10.4	32.0	25.0	20.4	15.7	18.2

Prevalence and intensities of helminth and *Plasmodium* spp. infections among 187 adults examined in the Taabo health demographic surveillance system, south-central Côte d'Ivoire, in June 2010. The thresholds of helminth infection intensities are in accordance with WHO guidelines provided in reference [11]. [a]Prevalence obtained by urine filtration method (one urine sample per person, single filtration). [b]Prevalence obtained by Kato-Katz method (one stool sample per person, duplicate Kato-Katz thick smears per sample). [c]Prevalence obtained by rapid diagnostic test (one rapid diagnostic test per person).

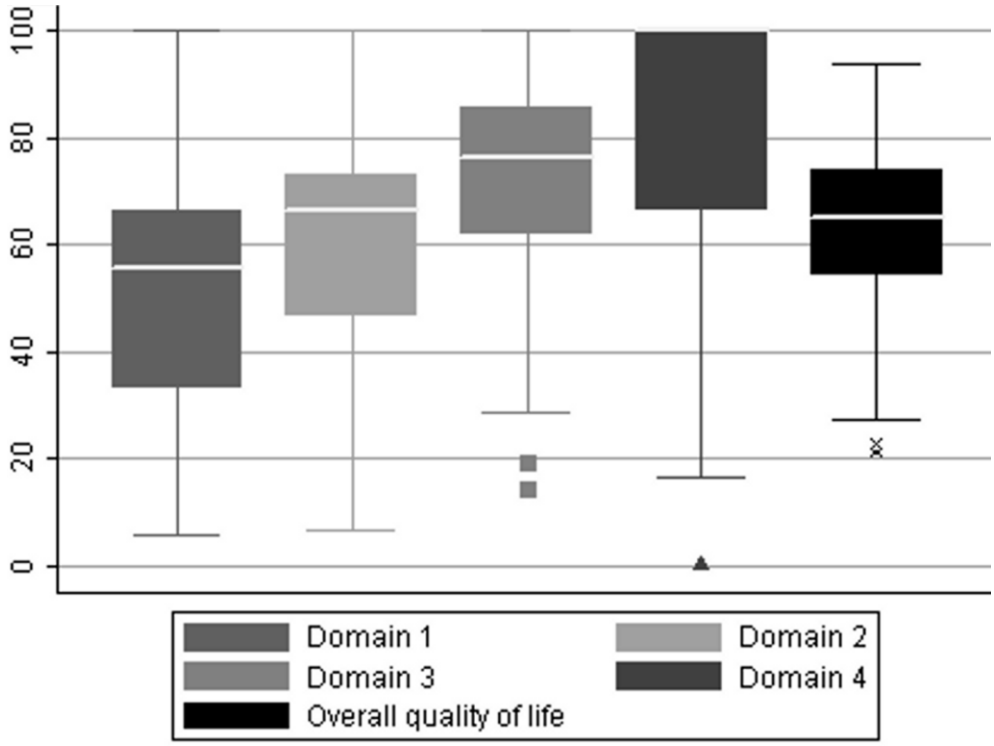

Figure 22. Box plots illustrating the different domain and overall quality of life scores as revealed in the present study. The study was carried out in June 2010, readily embedded in the second annual cross-sectional epidemiological survey of the Taabo health demographic surveillance system. The different domain and overall quality of life (QoL) scores were obtained through questionnaire-based QoL interviews with the study participants. The participants' scores were measured on a scale from 0 to 100, as detailed on the y-axis of the figure, with higher scores indicating higher well-being. Domain 1 = environmental well-being. Domain 2 = psychological well-being. Domain 3 = physical well-being. Domain 4 = social well-being. Box plot: the ends of the box represent the 25th and 75th percentile of the scores; the middle line represents the median; the lower whisker represents the lowest value between the lower quartile and the lower quartile - 1.5 * (interquartile range); the upper whisker represents the highest value between the upper quartile and the upper quartile + 1.5 * (interquartile range); the small squares, triangles, and crosses indicate outliers.

The wealth index ($p = 0.034$) and *S. mansoni* and *T. trichiura* infections of any intensity ($p = 0.011$ and $p = 0.035$, respectively) remained as the only three statistically significant explanatory variables for the overall QoL scores in the multivariable linear regression model with backward elimination (Table 29 and Appendix 13.5.4.). The other three remaining variables after backward elimination were sex ($p = 0.067$), working in the secondary or tertiary sectors ($p = 0.094$), and hookworm infection of any intensity ($p = 0.061$). Whether age and wealth were used as continuous variables (e.g., age in years and wealth as wealth index as in the presented model) or as categorical variables (e.g., age as age categories and/or wealth as wealth quintiles; details on these models are not shown) influenced these findings only insofar as the individuals' occupation was also eliminated in the latter models.

Table 28. Mean domain and overall quality of life scores in relation to socio-demographic determinants in rural Côte d'Ivoire.

Socio-demographic or parasitological determinants	Mean domain and overall quality of life score									
	Domain 1	p-value[a]	Domain 2	p-value[a]	Domain 3	p-value[a]	Domain 4	p-value[a]	Quality of life	p-value[a]
Sex: male	49.2		64.5		73.0		86.7		65.0	
Sex: female	52.1	0.275	60.5	0.180	69.5	0.267	83.7	0.496	62.8	0.385
Age: 18-40 years	48.9		63.5		74.0		87.6		65.2	
Age: 41-60 years	50.3		61.0		70.1		82.3		62.5	
Age: over 60 years	54.2	0.424	64.3	0.467	69.4	0.614	87.8	0.554	65.0	0.618
Education: no	51.1		62.7		68.9		87.8		63.3	
Education: primary school	45.9		62.6		76.6		83.8		64.7	
Education: secondary school	50.9		61.3		71.4		81.4		63.3	
Education: higher education	70.4	0.043*	68.9	0.859	77.0	0.423	80.6	0.234	73.0	0.393
Occupation: primary sector	48.3		61.9		70.5		84.8		62.8	
Occupation: secondary sector	56.9		64.2		70.8		91.7		66.1	
Occupation: tertiary sector	56.6	0.050	64.5	0.717	74.0	0.464	85.7	0.980	67.2	0.192
Socio-economic status: most poor	47.2		64.1		75.3		91.0		65.4	
Socio-economic status: very poor	46.6		59.8		72.6		82.4		62.6	
Socio-economic status: poor	47.2		61.8		65.9		85.5		60.6	
Socio-economic status: less poor	49.4		58.0		68.3		79.3		60.7	
Socio-economic status: least poor	62.6	0.006*	69.0	0.091	74.4	0.071	87.8	0.392	70.3	0.063
S. haematobium : negative	50.6		62.8		71.7		85.8		64.2	
S. haematobium : positive	47.2	0.926	50.0	0.168	56.0	0.126	62.5	0.375	51.9	0.223
S. mansoni: negative	50.9		62.8		71.7		85.8		64.3	
S. mansoni: positive	33.3	0.251	50.0	0.191	56.0	0.114	62.5	0.180	47.7	0.130
Hookworm: negative	54.4		62.6		71.9		87.9		65.4	
Hookworm: positive	44.6	0.002*	62.6	0.895	70.5	0.702	81.3	0.143	61.6	0.114
A. lumbricoides : negative	50.6		62.6		71.3		85.3		63.9	
A. lumbricoides : positive	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
T. trichiura : negative	64.4		77.3		79.1		93.3		75.8	
T. trichiura : positive	50.2	0.070	62.2	0.105	71.1	0.233	85.1	0.434	63.6	0.060
Plasmodium spp.: negative	50.2		62.6		70.8		85.8		63.8	
Plasmodium spp.: positive	52.1	0.514	62.6	0.979	73.5	0.510	82.8	0.308	64.7	0.494

Mean domain and overall quality of life scores in relation to socio-demographic determinants among 187 adults in the Taabo health demographic surveillance system, south-central Côte d'Ivoire, in June 2010. Domain 1 = environmental well-being. Domain 2 = psychological well-being. Domain 3 = physical well-being. Domain 4 = social well-being. NA = not applicable. [a]p-values from comparing mean scores by using Wilcoxon rank sum and Kruskal-Wallis tests as appropriate. *Statistically significant ($p < 0.05$).

Table 29. Associations remaining in the multivariable linear regression model after stepwise backward elimination.

Explanatory variable	Coeff.	95% CI	p-value
Sex[a]	-3.5	(-7.3, 0.2)	0.067
Working in secondary or tertiary sectors[b]	3.8	(-0.7, 8.3)	0.094
Wealth index[c]	1.2	(0.1, 2.3)	0.034*
S. mansoni infection of any intensity[d]	-16.4	(-29.2, -3.7)	0.011*
Hookworm infection of any intensity[e]	-3.9	(-8.0, 0.2)	0.061
T. trichiura infection of any intensity[f]	-12.6	(-24.4, -0.9)	0.035*

A multivariable linear regression model with a stepwise backward elimination procedure was adopted in order to identify those explanatory variables, which most significantly influence the study participants' quality of life (QoL) scores. The explanatory variables and indicators of the multivariable linear regression model at each step of the backward elimination procedure are shown in the supporting information (Appendix 13.5.4.). The data on socio-demographic factors, parasitology, and QoL of the 187 study participants were collected in the Taabo health demographic surveillance system, south-central Côte d'Ivoire, in June 2010. CI = confidence interval. [a]Reference category: male. [b]Reference category: primary sector. [c]Continuous variable. [d]Reference category: no *S. mansoni* infection. [e]Reference category: no hookworm infection. [f]Reference category: no *T. trichiura* infection. *Statistically significant ($p < 0.05$).

9.5.4. Attrition analysis

Comparison of participants who were included in the final analysis and participants who gave written informed consent and completed the questionnaire, but dropped out due to incomplete parasitological data, revealed no statistically significant differences in socio-demographic characteristics (Table 30) or mean domain and overall QoL scores (Table 31). Moreover, our attrition analysis revealed no significant difference between included and excluded people in terms of mean domain and overall QoL scores.

Table 30. Attrition analysis comparing socio-demographic determinants between included and excluded individuals.

Socio-demographic factor	Included (n = 187)	Excluded (n = 61)	p-value[a]
Sex: male	98	25	
Sex: female	89	36	0.121
Age: 18-40 years	66	27	
Age: 41-60 years	84	28	
Age: over 60 years	37	6	0.163
Education: no	100	34	
Education: primary school	39	18	
Education: secondary school	42	8	
Education: higher education	6	1	0.277
Occupation: primary sector	136	50	
Occupation: secondary sector	8	0	
Occupation: tertiary sector	43	11	0.164
Socio-economic status: most poor	33	18	
Socio-economic status: very poor	35	14	
Socio-economic status: poor	42	8	
Socio-economic status: less poor	39	10	
Socio-economic status: least poor	38	11	0.189

The socio-demographic determinants of the 248 individuals who participated in the questionnaire survey were collected in the Taabo health demographic surveillance system, south-central Côte d'Ivoire, in June 2010. [a]p-values from comparing the number of included individuals *vs.* the number of excluded individuals with a specific socio-demographic determinant by using χ^2 and Fisher's exact test, as appropriate.

Table 31. Attrition analysis comparing mean domain and overall quality of life scores between included and excluded individuals.

Quality of life indicator	Included (n = 187)	Excluded (n = 61)	p-value[a]
Domain 1: environmental well-being	50.6	49.6	0.770
Domain 2: psychological well-being	62.6	60.9	0.464
Domain 3: physical well-being	71.3	68.0	0.213
Domain 4: social well-being	85.3	83.3	0.632
Overall quality of life	63.9	62.3	0.468

The domain and overall quality of life (QoL) scores of the 248 individuals who participated in the questionnaire survey were collected in the Taabo health demographic surveillance system, south-central Côte d'Ivoire, in June 2010. [a]p-values from comparing the mean domain and overall QoL scores between included and excluded individuals by using Wilcoxon rank sum test.

9.6. Discussion

We present an analysis from a QoL questionnaire survey conducted alongside the 2010 cross-sectional epidemiological survey and deworming campaign in the Taabo HDSS in south-central Côte d'Ivoire. Results of a multivariable linear logistic regression model revealed that adults' QoL is reduced considerably among those infected with different species of helminths, regardless of the intensity of infection. Indeed, we found that the perceived QoL among adults infected with *S. mansoni* and *T. trichiura* was 16 points (95% confidence interval (CI): 4-29 points) and 13 points (95% CI: 1-24 points) lower on a scale from 0 to 100 than the reported QoL of non-infected individuals. The only other statistically significant effect was a 1-point (95% CI: 0.1-2 points) increase in QoL per one unit increase in the wealth index. Other important explanatory variables that remained in our multivariable linear regression model after applying a stepwise backward elimination procedure were sex, indicating a 4 points (95% CI: 27-0.2 points) decrease in QoL of females; occupation, indicating a 4 points (95% CI: 20.7-8 points) increase in QoL of those working mainly in the secondary or tertiary sectors; and hookworm infections, indicating a 4 points (95% CI: 28-0.2 points) decrease in QoL of those infected.

Our results have to be interpreted with caution, but raise many interesting issues. As a first critical point, it has to be considered that the sampling of the current study depended on a stratified random sampling. Starting in mid-2009, our team pursued a yearly cross-sectional epidemiological survey among approximately 7% of the people who were under demographic and health surveillance in the Taabo HDSS. The present study was linked to the June 2010 cross-sectional survey, using a sub-sample (i.e., all head of households plus a second randomly selected person of the same household but the opposite sex to maintain gender balance). Given our sampling approach and in view of operational and financial considerations, no formal sample size calculation was made for the present study.

Second, our final sample size of 187 individuals was relatively small and the compliance rate of 73.3% suboptimal. However, somewhat higher drop-out rates had to be expected as the participants were adults, many of whom were illiterate. Compared to school-aged children, adults seemed to be somewhat reluctant or ashamed to provide any stool or urine samples. Importantly though, the attrition analysis revealed no statistically significant differences in the available indicators between the included and excluded adults, and hence no selection bias seems to have been introduced by the drop-outs.

Third, the absence of a statistically significant inter-observer variation suggests that our questionnaire results are reliable. Cronbach's alpha as well as the highly significant positive

correlation between the calculated summary scores on QoL based on all questions and the QoL ratings directly expressed by the participants in the final question of the questionnaire indicate internal consistency and validity of the QoL scores.

Fourth, the parasitological diagnosis was based on single stool and urine samples with duplicate Kato-Katz thick smear examinations and single urine filtration, respectively. There is a large body of work demonstrating that multiple sampling or a combination of diagnostic methods result in more accurate diagnosis.[29,30] It follows that we missed some helminth infections, particularly those of light intensity. At this stage, it is difficult to say how these false negative results might have influenced our findings. However, assuming that helminth infections have no beneficial impact on patients' QoL, one hypothesis would be that the false negative results mistakenly lowered the QoL of the uninfected comparison group in our study. Furthermore, assuming that most individuals with false negative results suffered from light infections (like most of those effectively diagnosed as infected), a next hypothesis is that false negative results do not systematically distort the QoL of the infected comparison group. This hypothesis would even hold true when expecting a correlation between infection intensity and QoL. One could therefore argue that the false negative results may have mistakenly reduced the measured QoL difference between the uninfected and infected comparison group in our study.

Fifth, the mean domain and overall QoL scores displayed in Table 28 were consistently lower in participants with helminth infections compared to their helminth-free counterparts. For instance, participants tested positive for *S. mansoni* reported a statistically non-significant, but consistent decrease in the mean environmental ($p = 0.251$), psychological, physical, and social well-being (all $p < 0.2$). This remarkable consistency increases the plausibility of the presented findings. However, with regard to *Plasmodium* spp. infections the picture was less clear. Participants with positive malaria RDTs reported higher mean scores on environmental and physical well-being and had higher overall QoL score. These counterintuitive findings might at least partially be explained by false positive results of the RDTs because of delayed clearance of the circulating antigen[31] and by the acquired semi-immunity of probably all examined adults leading to usually uncomplicated malaria with mild symptoms.[32]

Sixth, the effects of the socio-demographic determinants on the mean domain and overall QoL scores were somewhat less clear in the univariable comparison as summarized in Table 28. However, the statistically significantly higher scores in environmental well-being of higher educated adults and the wealthiest participants demonstrate also the unsurprising importance of socio-demographic determinants. This statement is supported by the fact that

sex, the sector of occupation, and the wealth index also remained in the multivariable linear regression model after the stepwise backward elimination.

Seventh, there were only a few people infected with *S. haematobium*, *S. mansoni*, and *T. trichiura* in our study sample and even though the probably most obvious confounders (e.g., age, sex, educational attainment, occupation, and socio-economic status) were included in our analyses, we cannot rule out an effect of other potential confounders (e.g., lack of access to clean water and sanitation). Furthermore, we did not consider infection intensities or explore interaction terms for combined infections in our multivariable linear regression model as more complex modeling was not possible due to the comparatively small numbers.

Eighth, the here presented decrease of 16 points on the 0 to 100 QoL scale due to *S. mansoni* infections can be interpreted as a disability of 16%. This disability estimate is slightly below previously presented results from QoL surveys on advanced, chronic *S. japonicum* in the People's Republic of China, which revealed a mean disability of 19%[7] and up to even 45%[10]. However, our results are considerably higher than current WHO estimates, which indicate a disability of only 1% for any *Schistosoma* infection and 10% for advanced renal or hepatic infection.[33] Unfortunately, no QoL surveys for comparison could be identified with regard to soil-transmitted helminth infections. However, if the 13 points reduction for *T. trichiura* infections and the 4 points reduction for hookworm infections are also considered as disabilities of 13% and 4%, they are in the range of the disability weights listed by WHO (trichuriasis-associated high intensity infection 0%, contemporaneous cognitive deficit 1%, massive dysentery syndrome 12%, and cognitive impairment 2%; hookworm-associated high intensity infection 1%, anemia 2%, and cognitive impairment 2%).[33]

In conclusion, we found consistent and significant results on the effect of schistosomiasis, soil-transmitted helminthiasis, and socio-demographic determinants on adults' QoL in rural Côte d'Ivoire. It is conceivable that helminth-infected adults in the present study suffered from advanced chronic infections and therefore reported notable losses in QoL. Our results warrant further investigation on the disability induced by helmintic infections and further probing of the usefulness and applicability of generic QoL questionnaires in this regard. Future studies should adhere to a more rigorous sampling strategy and sample size calculation, optimally in a randomized trial design, which allows for an improved control of potential confounders and the assessment of interactions due to combined infections. Furthermore, they should consider additional qualitative research to further explore the local residents' concept about QoL, additional verification of the QoL questionnaire's reliability and validity (e.g.,

test-retest comparison, comparison of questionnaire results with objectively measurable indicators[9]), more intensive parasitological diagnosis (e.g., repeated stool, urine, and blood sampling, multiple testing, and concurrent use of different diagnostic methods), further analyses regarding the effects of differing infection intensities, and clinical examinations (e.g., stethoscopy and ultrasound) to confirm chronic sequelae and other medical complaints.

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10. Scope and limits of an anamnestic questionnaire in a control-induced low-endemicity helminthiasis setting in south-central Côte d'Ivoire

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10.1. Abstract

Background: Schistosomiasis and soil-transmitted helminthiasis are two high-burden neglected tropical diseases. In highly endemic areas, control efforts emphasize preventive chemotherapy. However, as morbidity, infection, and transmission begin to decrease, more targeted treatment is likely to become more cost-effective, provided that comparatively cheap diagnostic methods with reasonable accuracy are available.

Methodology: Adults were administered an anamnestic questionnaire in mid-2010 during a cross-sectional epidemiological survey in the Taabo health demographic surveillance system in south-central Côte d'Ivoire. Questions pertaining to risk factors and signs and symptoms for schistosomiasis and soil-transmitted helminthiasis were included. The individuals' helminth infection status and their belonging to three different anthelmintic treatment groups were compared with the questionnaire results (i) to inform the local health authorities about the epidemiological and clinical footprint of locally prevailing helminthiases, and (ii) to explore the scope and limits of an anamnestic questionnaire as monitoring tool, which eventually could help guiding the control of neglected tropical diseases in control-induced low-endemicity settings.

Principal findings: Our study sample consisted of 195 adults (101 males, 94 females). We found prevalences of hookworm, *Trichuris trichiura*, *Schistosoma haematobium*, and *Schistosoma mansoni* of 39.0%, 2.7%, 2.1%, and 2.1%, respectively. No *Ascaris lumbricoides* infection was found. Helminth infection intensities were generally very low. Seven, 74 and 79 participants belonged to three different treatment groups. Multivariable logistic regression models revealed statistically significant ($p < 0.05$) associations between some risk factors, signs, and symptoms, and the different helminth infections and treatment groups. However, the risk factors, signs, and symptoms showed weak diagnostic properties.

Conclusions/Significance: The generally low prevalence and intensity of helminth infection in this part of south-central Côte d'Ivoire indicates that recent control efforts have turned our study area into a low endemicity setting. Our anamnestic questionnaire had low sensitivity and specificity to identify infected individuals or treatment groups.

Keywords: Schistosomiasis, soil-transmitted helminthiasis, anamnestic questionnaire, helminthiasis control, Côte d'Ivoire.

10.2. Introduction

Schistosomiasis and soil-transmitted helminthiasis are two high burden neglected tropical diseases.[1] Burden estimates, as expressed in disability-adjusted life years (DALYs), range from 1.7 to 70 million DALYs for schistosomiasis,[1-8] and from 2.9 to 39 million DALYs for soil-transmitted helminthiasis.[1,3,4,8,9] The awareness for these high disease burdens have increased in the past few years, but despite the fact that control efforts are going to scale, a variety of high and low endemicity zones remain around the globe.[10,11]

The main strategy to combat the diseases in highly endemic areas is morbidity control. Once morbidity has decreased, the control strategies foresee a progressive shift toward infection and transmission control, surveillance and case detection and, ultimately, local elimination.[12-14] Consequently, the diagnosis, treatment, and control strategies have to be adapted.[13,15,16] For instance, in high endemicity areas, preventive chemotherapy (i.e., regular treatment of high-risk groups without prior diagnosis[17]) using available, safe, and efficacious drugs that are inexpensive or donated by pharmaceutical companies, is the most widely used strategy.[17,18] However, as morbidity, infection, and transmission begin to decrease, more targeted treatment might become more cost-effective,[19] provided that comparatively cheap diagnostic methods with reasonable accuracy are available.[13] Such diagnostics have to consider the changes in parasite ecology that increasingly occur due to the scale-up of preventive chemotherapy and the expansion of more integrated control strategies, which tackle multiple helminth species simultaneously[18,20] and also on non-drug-based routes (e.g., providing clean water and improved sanitation).[21,22] Hence, control-induced low-endemicity settings have become the new reality of helminth epidemiology in many areas.

Simple, rapid, inexpensive, and culturally adapted questionnaires have been considered as useful diagnostic tools to screen communities and guiding control interventions over the past years.[23] Regarding schistosomiasis, for example, school-based questionnaires proved useful for identification of high-risk communities of *Schistosoma haematobium*.[24] Indeed, school prevalence of self-reported blood in urine correlates well with the prevalence of *S. haematobium*.[24] A simple anamnestic questionnaire, including questions on signs, symptoms, and water contact patterns, allowed individual diagnosis of *S. japonicum*.[25] However, adaptation for *S. mansoni* and other helminth infections proved to be more difficult[13,24,26] and the usefulness of anamnestic questionnaires seems to be restrained in regions with naturally low helminth endemicity as noticeable signs and symptoms are rare. Further research is therefore needed to determine the scope and limits of anamnestic

questionnaires when they are employed over the course of control programs, which are characterized by declining morbidity and prevalence rates.[13,23,27]

In this paper, we report our experience from a cross-sectional survey carried out in mid-2010 as part of a prospective longitudinal monitoring of people's malaria and neglected tropical diseases status in the Taabo health demographic surveillance system (HDSS) in south-central Côte d'Ivoire. The study area represents an epidemiological situation, which is influenced by helminth control activities.[28] The two objectives of the survey were (i) to assess risk factors, signs, and symptoms related to schistosomiasis and soil-transmitted helminthiasis in order to inform the local health authorities about the epidemiological and clinical footprint of these two helminthiasis, and (ii) to explore the scope and limits of an anamnestic questionnaire as monitoring tool, which eventually could help guiding the control of neglected tropical diseases in control-induced low-endemicity settings.

10.3. Methods

10.3.1. Ethics statement

The study protocol was cleared by the institutional research commissions of the Centre Suisse de Recherches Scientifiques en Côte d'Ivoire (CSRS; Abidjan, Côte d'Ivoire) and the Swiss Tropical and Public Health Institute (Swiss TPH; Basel, Switzerland). Ethical clearance was obtained from the Comité National d'Ethique et de la Recherche (CNER) in Côte d'Ivoire (reference no. 1086 MSHP/CNER) and the ethics committee in Basel (EKBB; reference no. 316/08).

The study was integrated in the second annual parasitological survey and preventive chemotherapy campaign in the Taabo HDSS in June 2010. District and village authorities and the general public were informed about the purpose, procedures, potential risks and benefits of the annual survey, treatment, and the current questionnaire study. Written informed consent was obtained from all participants of the present study. Everybody living in the area of the Taabo HDSS was invited for a free anthelmintic treatment with ivermectin (~200 μg/kg using a dose pole) and albendazole (400 mg single oral dose), irrespective of the infection status or participation in the present study.[29,30] Praziquantel (40 mg/kg using a dose pole), was administered half a year later for individuals aged 5 years and above in the course of a preventive chemotherapy campaign against schistosomiasis.[29] Medical staff accompanied the survey, anthelmintic treatment, and follow-up.

10.3.2. Study area and population

The study area and population have been described elsewhere.[31] In brief, the Taabo HDSS was established in 2008 around Lake Taabo in south-central Côte d'Ivoire. It covers most of the rural sub-district of Taabo with a surface area of approximately 1,000 km^2. Since 2012, the Taabo HDSS is a member center of the INDEPTH Network (see http://www.indepth-network.org). The main station of the Taabo HDSS is located in Taabo Cité, the only small urban settlement in the Taabo HDSS, 160 km north-west of Abidjan. Most people in the region cultivate yams, manioc, and banana mainly for subsistence. Coffee and cacao are farmed as cash crops. Furthermore, there is a minority of fishermen, artisans, shopkeepers, and businessmen.

Lake Taabo is a man-made impoundment resulting from damming up the Bandama River in the late 1970s for hydroelectric power generation.[32] Hence, the study area underwent major ecologic and demographic transformation, which favored the spread of schistosomiasis[32,33] and might have influenced patterns of other helminth infections[34,35] and malaria.[36] Before the establishment of the Taabo HDSS, different studies provided sporadic anthelmintic treatment to some village communities. Therefore, the development of more systematic and integrated disease control measures, particularly annual preventive chemotherapy campaigns against helminthiases and a strengthening of the health system became specific objectives of the Taabo HDSS.

10.3.3. Data collection

The parasitological data for the present study were obtained in the frame of the second cross-sectional survey and preventive chemotherapy campaign (carried out once every year) in the Taabo HDSS. While everybody living in the area of the Taabo HDSS was invited to participate in the preventive chemotherapy campaign, the members of approximately 7% of all registered households were selected for the epidemiological survey based on a stratified random sampling procedure. They were asked to provide fresh morning stool and urine samples. The samples were transferred to the laboratory of the general hospital in Taabo Cité and analyzed the same day by experienced laboratory technicians using standardized, quality-controlled techniques.[37,38] In short, duplicate Kato-Katz thick smears were prepared with 41.7 mg of stool and microscopically examined for *S. mansoni* and soil-transmitted helminths (*Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm). In order to obtain infection intensities as expressed in eggs per gram of stool (EPG), the sum of the helminth-specific egg

counts from the two Kato-Katz thick smears were multiplied by a factor 12.[29] Urine samples were vigorously shaken, 10 ml subjected to a filtration, and the filters, after adding a drop of iodine Lugol, microscopically examined for *S. haematobium*. Five percent of the Kato-Katz thick smears and the urine filters were re-examined by a senior technician. In case of disagreement, the slides were read a third time and the results discussed among the technicians until agreement was reached.

All heads of households and, if possible, a second adult household member of the opposite sex were eligible for the present study. On the day of the epidemiological survey, all eligible individuals were invited to complete a questionnaire on risk factors, signs, and symptoms pertaining to different neglected tropical diseases (Appendix 13.6.1.) with the assistance of a trained field enumerator or supervisor of the Taabo HDSS. Questions were either asked in French or translated and explained in any of the local languages (Baoulé, Dioula, or Senoufo). Our questionnaire was carefully developed from previously employed questionnaires in Côte d'Ivoire,[39-42] further adapted during discussions with health personnel and Taabo HDSS staff and pre-tested in a nearby village.

Additional socio-demographic data on the individual and household level, including information on sex, age, education, main occupation, relationship with the respective head of household, type of housing, and availability of facilities were readily available from the Taabo HDSS database. For further details on the field and laboratory procedures, the reader is referred to Fürst *et al.* (2012).[31] All data from the present study can be obtained from the authors upon request.

10.3.4. Statistical analysis

Data were double-entered and cross-checked in EpiInfo version 3.5.1 (Centers for Disease Control and Prevention; Atlanta, United States of America), and analyzed in STATA version 10.1 (STATA Corp.; College Station, United States of America). Participants for the present study were purposefully sampled, as described in the previous section, with no formal sample size calculation. Only individuals with complete datasets were included in our final analysis.

Age was stratified into three groups, namely (i) 18-40 years, (ii) 41-60 years, and (iii) > 60 years. Educational levels were classified as (i) none, (ii) primary, and (iii) secondary or higher. Occupation was grouped into farmer, fisherman and hunter, housewife, builder and artisan, and being employed in the tertiary sector (includes driver, housekeeper, watchman, merchant, trader, hairdresser, gastronome, healer, nurse, teacher, student, office worker, and

policeman). The parasitological results were classified according to infection intensities as expressed in EPG (for *S. mansoni* and soil-transmitted helminths) and eggs/10 ml of urine (for *S. haematobium*), according to World Health Organization (WHO) guidelines.[29] Furthermore, treatment groups were established, relying on the parasitological results and current WHO recommendations,[18] i.e., *S. haematobium* and *S. mansoni* infections in the praziquantel treatment group (Tx1), *A. lumbricoides*, *T. trichiura*, and hookworm infections in the benzimidazole treatment group (Tx2), and all single or multiple infections with *S. haematobium*, *S. mansoni*, *A. lumbricoides*, *T. trichiura*, and hookworm in the overarching praziquantel and benzimidazole treatment group (Tx3).

Initially, χ^2 test statistics and Fisher's exact test, as appropriate, were used to identify univariable associations between helminth infections and treatment groups, respectively, and reported risk factors, signs, and symptoms. Risk factors, signs, and symptoms significantly associated ($p < 0.05$) were then included as explanatories in a multivariable logistic regression, again with the outcomes helminth infections and treatment groups. A stepwise backward elimination procedure was performed, removing the explanatory variable with the highest p-value one after the other, as long as the Akaike information criterion (AIC) was decreasing. Associations between anamnestic questions and treatment groups were considered as the correct treatment may be more important than exact species identification for control program managers.

Either each of the remaining and significantly associated ($p < 0.05$) explanatories on their own or all of them combined were used as diagnostic variables to predict helminth infections and treatment group specific classifications of individuals. In case of combining diagnostic variables, a scoring approach was adopted. All significantly associated risk factors, signs, and symptoms were coded 0 or 1 with the higher score indicating elevated odds for being infected with the respective helminth or belonging to a certain treatment group. The scores from all significantly associated risk factors, signs, and symptoms were then summed up to obtain each participant's combined score. Sensitivity (i.e., proportion of true-positives recognized as positives), specificity (i.e., proportion of true-negatives recognized as negatives), positive predictive value (PPV; i.e., probability that a positively tested individual is a true-positive), and negative predictive value (NPV; i.e., probability that a negatively tested individual is a true-negative) were used to assess the diagnostic performance of each significantly associated risk factor, sign, and symptom on its own and of the combined score at different cut-off levels.

10.4. Results

10.4.1. Study cohort and compliance

Details of our study cohort have been described elsewhere.[31] Overall, 255 adults were invited (128 males and 127 females; Figure 23). Sixty individuals were excluded (27 males and 33 females); seven had no written informed consent or failed to have complete questionnaire results, whereas 53 had no valid results from the parasitological examination, mainly because they lacked sufficiently large stool and/or urine samples for diagnostic workup. Our final study sample consisted of 195 adults (101 males and 94 females) with details of the socio-demographic characteristics summarized in Table 32.

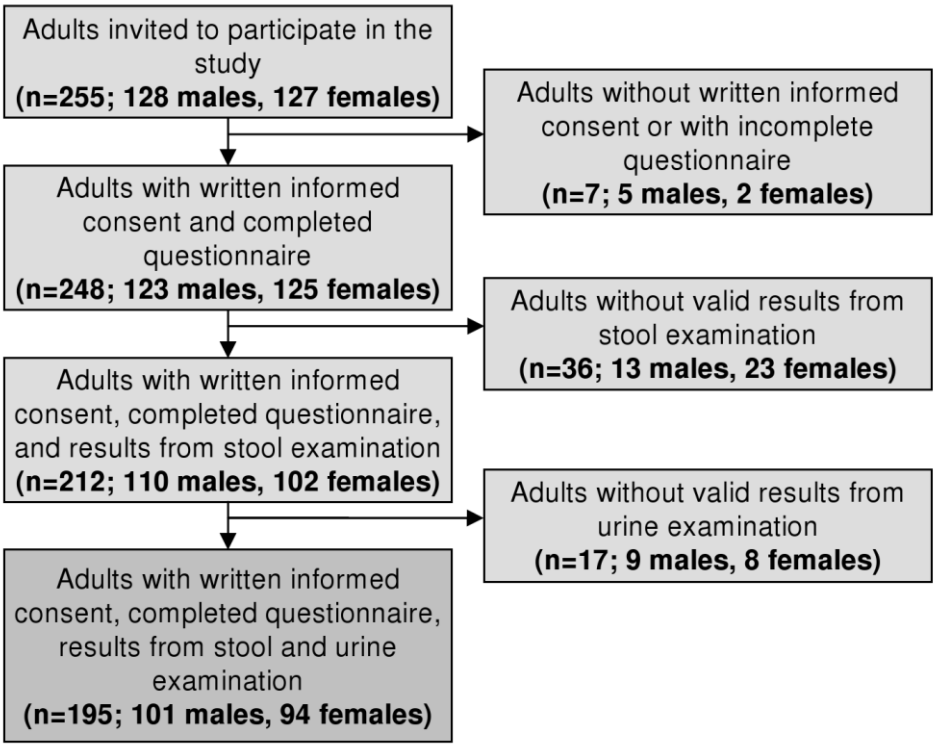

Figure 23. Study participation and compliance. The study was carried out in June 2010 in the Taabo health demographic surveillance system, south-central Côte d'Ivoire.

Table 32. Socio-demographic characteristics among the 195 study participants with complete questionnaire and parasitological data.

Socio-demographic characteristics		Number of people (%)
Sex	Male	101 (51.8)
	Female	94 (48.2)
Age (years)	18-40	107 (54.9)
	41-60	66 (33.9)
	>60	22 (11.3)
Education	None	106 (54.4)
	Primary	41 (21.0)
	Secondary or higher	48 (24.6)
Main occupation	Farmer	123 (63.1)
	Tertiary sector[a]	49 (25.1)
	Housewife	13 (6.7)
	Builder and artisan	8 (4.1)
	Fisherman and hunter	2 (1.0)

The study was carried out in June 2010 in the Taabo health demographic surveillance system, south-central Côte d'Ivoire. [a]Including driver, housekeeper, watchman, merchant, trader, hairdresser, gastronome, healer, nurse, teacher, student, office worker, and policeman.

10.4.2. Parasitological results

Table 33 shows the parasitological results. We found very low prevalence for *S. haematobium* and *S. mansoni* (2.1% for each schistosome species). The prevalence for hookworm and *T. trichiura* were 38.5% and 2.6%, whereas no *A. lumbricoides* were found. Most helminth infections were of low intensity. Seven, 76 and 81 participants belonged to Tx1, Tx2, and Tx3, respectively.

10.4.3. Results from univariable analysis

Based on univariable χ^2 test statistics and Fisher's exact test, we identified one risk factor and one symptom that were significantly associated with *S. haematobium* infection, three risk factors that were significantly associated with *S. mansoni*, 18 risk factors that were significantly associated with hookworm infection, and two risk factors that were significantly associated with *T. trichiura* infections (Table 34). Four risk factors and two symptoms were significantly associated with Tx1, 18 risk factors with Tx2, and 11 risk factors with Tx3, as shown in Table 35.

Table 33. Prevalence and intensity of helminth infections among the 195 study participants.

Parasite	Infection intensity[a]	Number of people (%)
Schistosoma haematobium	Negative	191 (97.9)
	Light	4 (2.1)
	Heavy	0
Schistosoma mansoni	Negative	191 (97.9)
	Light	3 (1.6)
	Moderate	1 (0.5)
	Heavy	0
Tx1 (Sh + Sm)	Negative	188 (96.4)
	Positive	7 (3.6)
Hookworm	Negative	120 (61.5)
	Light	72 (36.9)
	Moderate	3 (1.6)
	Heavy	0
Trichuris trichiura	Negative	190 (97.4)
	Light	4 (2.1)
	Moderate	1 (0.5)
	Heavy	0
Ascaris lumbricoides	Negative	195 (100.0)
	Light	0
	Moderate	0
	Heavy	0
Tx2 (Hw + Tt + Al)	Negative	119 (61.0)
	Positive	76 (39.0)
Tx3 (Sh + Sm + Hw + Tt + Al)	Negative	114 (58.5)
	Positive	81 (41.5)

The study was carried out in June 2010 in the Taabo health demographic surveillance system, south-central Côte d'Ivoire. Al = *A. lumbricoides*. Hw = hookworm. Sh = *S. haematobium*. Sm = *S. mansoni*. Tt = *T. trichiura*. Tx1 = treatment group 1 (i.e., praziquantel against schistosomiasis). Tx2 = treatment group 2 (i.e., benzimidazole against soil-transmitted helminthiasis). Tx3 = treatment group 3 (i.e., praziquantel and benzimidazole against schistosomiasis and soil-transmitted helminthiasis, respectively). [a]Infection intensities according to WHO guidelines.[29]

Table 34. Risk factors, signs, and symptoms significantly ($p < 0.05$) associated with helminth infections, as determined by univariable analysis.

Parasite	Risk factor, sign, and symptom	p-value[a]
Schistosoma haematobium	Vertigo	0.026
	Worm infections considered frequent in household	0.027
Schistosoma mansoni	Occupation: farmer	0.018
	Occupation: housewife	0.023
	Drinking water: rain	0.011
Hookworm	Occupation: farmer	0.022
	Occupation: tertiary sector	0.027
	Tile or carpet flooring	0.011
	Type of toilet: WC	0.048
	Open defecation	0.014
	Natural water contact: washing oneself	0.010
	Natural water contact: cooking	0.014
	Natural water contact: washing children	0.033
	Natural water contact: cultivating rice	0.019
	Natural water contact: religious worship	0.045
	Drinking water: natural water body	0.001
	Drinking water: rain	0.042
	Drinking water: fountain	0.011
	Using soap for washing clothes	0.015
	Using soap for washing dishes	0.024
	Washing hands after defecation	0.003
	Washing hands when returning from work	0.004
	Worm infections considered frequent in household	0.003
Trichuris trichiura	Using soap for washing oneself	0.018
	Having a cat	0.048

The study was carried out in June 2010 in the Taabo health demographic surveillance system, south-central Côte d'Ivoire. [a]Univariable analysis, using χ^2 test statistics and Fisher's exact test, as appropriate.

Table 35. Risk factors, signs, and symptoms significantly ($p < 0.05$) associated with treatment groups, as determined by univariable analysis.

Treatment group	Risk factor, sign, and symptom	p-value[a]
Tx1	Occupation: farmer	0.011
	Occupation: builder and artisan	0.028
	Drinking water: rain	0.005
	Headache	0.049
	Vertigo	0.018
	Worm infections considered frequent in household	0.020
Tx2	Occupation: farmer	0.015
	Occupation: tertiary sector	0.018
	Tile or carpet flooring	0.010
	Type of toilet: WC	0.047
	Open defecation	0.022
	Natural water contact: washing oneself	0.010
	Natural water contact: cooking	0.022
	Natural water contact: washing children	0.035
	Natural water contact: cultivating rice	0.010
	Drinking water: natural water body	0.001
	Drinking water: rain	0.042
	Drinking water: fountain	0.017
	Using soap for washing clothes	0.015
	Using soap for washing dishes	0.025
	Washing hands after defecation	0.005
	Washing hands when returning from work	0.004
	Having poultry	0.043
	Worm infections considered frequent in household	0.004
Tx3	Occupation: tertiary sector	0.044
	Tile or carpet flooring	0.009
	Uncemented latrine	0.028
	Natural water contact: washing oneself	0.011
	Natural water contact: cultivating rice	0.011
	Drinking water: natural water body	0.003
	Drinking water: fountain	0.018
	Using soap for washing clothes	0.018
	Washing hands after defecation	0.005
	Washing hands when returning from work	0.002
	Worm infections considered frequent in household	0.002

The study was carried out in June 2010 in the Taabo health demographic surveillance system, south-central Côte d'Ivoire. Tx1 = treatment group 1 (i.e., praziquantel against schistosomiasis). Tx2 = treatment group 2 (i.e., benzimidazole against soil-transmitted helminthiasis). Tx3 = treatment group 3 (i.e., praziquantel and benzimidazole against schistosomiasis and soil-transmitted helminthiasis, respectively). [a]Univariable analysis, using χ^2 test statistics and Fisher's exact test, as appropriate.

10.4.4. Results from multivariable analysis

Many of the univariably significantly associated risk factors, signs, and symptoms presented in Tables 34 and 35 dropped out when subjecting them to multivariable logistic regression with a stepwise backward elimination procedure, as shown in Table 36. The only remaining significant explanatory variable for *S. mansoni* infection was being a housewife (odds ratio (OR) = 10.3, 95% confidence interval (CI): 1.1-102.1), whereas all explanatories for *S. haematobium* were eliminated. People belonging to the praziquantel treatment group (Tx1) had an increased risk for vertigo (OR = 16.9, 95% CI: 1.2-34.6).

People cultivating rice (OR = 2.6, 95% CI: 1.2-5.7) and considering worm infections as something that occurs frequently in their household (OR = 4.6, 95% CI: 1.4-14.6) were at a higher risk for hookworm infection. On the other hand, people who use fountains as a primary source of drinking water (OR = 0.4, 95% CI: 0.2-0.8) and those who use soap for washing clothes (OR = 0.1, 95% CI: 0.02-0.6) had low odds of hookworm infection. Regarding *T. trichiura*, having a cat as domestic animal was associated with a high odds of infection (OR = 10.6, 95% CI: 1.3-85.8), whereas using soap for washing oneself showed a low odds of infection (OR = 0.05, 95% CI: 0.01-0.4). People cultivating rice (OR = 2.9, 95% CI: 1.3-6.4) and considering worm infections as something that occurs frequently in their household (OR = 4.4, 95% CI: 1.4-14.1) showed higher odds and people reporting fountains as an important source of drinking water (OR = 0.4, 95% CI: 0.2-0.9), using soap for washing clothes (OR = 0.1, 95% CI: 0.02-0.6), and washing their hands when returning from work (OR = 0.5, 95% CI: 0.2-0.9) had lower odds to belonging to the benzimidazole treatment group (Tx2).

Cultivating rice (OR = 2.8, 95% CI: 1.3-6.2) or considering worm infections as frequent in the household (OR = 5.4, 95% CI: 1.7-17.9) were associated with high odds, whereas fountains as an important source of drinking water (OR = 0.4, 95% CI: 0.2-0.8), using soap for washing clothes (OR = 0.1, 95% CI: 0.02-0.8), or washing hands when returning from work (OR = 0.4, 95% CI: 0.2-0.8) were associated with low odds of schistosomiasis and soil-transmitted helminthiasis, and therefore belonging to the treatment group Tx3.

Table 36. Risk factors, signs, and symptoms significantly ($p < 0.05$) associated with parasites and treatment groups, as determined by multivariable logistic regression modeling.

Parasite or treatment group	Risk factor, sign, and symptom	Adjusted odds ratio (95% CI)	Sensitivity in % (95% CI)	Specificity in % (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
S. mansoni	Housewife	10.3 (1.1, 102.1)	50.0 (43.0, 57.0)	94.2 (91.0, 97.5)	15.4 (10.3, 20.5)	98.9 (97.4, 100.0)
Hookworm	Natural water contact: cultivating rice	2.6 (1.2, 5.7)	29.3 (22.9, 35.7)	85.0 (80.0, 90.0)	55.0 (48.0, 62.0)	65.8 (59.2, 72.5)
	Drinking water: fountain	0.4 (0.2, 0.8)	29.3 (22.9, 35.7)	51.7 (44.6, 58.7)	27.5 (21.2, 33.8)	53.9 (46.9, 60.9)
	Using soap for washing clothes	0.1 (0.02, 0.6)	89.3 (85.0, 93.7)	1.7 (0.1, 3.5)	36.2 (29.5, 43.0)	20.0 (14.4, 25.6)
	Worm infections considered frequent in household	4.6 (1.4, 14.6)	18.7 (13.2, 24.1)	95.0 (91.9, 98.1)	70.0 (63.6, 76.4)	65.1 (58.5, 71.8)
T. tichiura	Using soap for washing oneself	0.05 (0.01, 0.4)	60.0 (53.1, 66.9)	3.7 (1.0, 6.3)	1.6 (0.1, 3.4)	77.8 (71.9, 83.6)
	Having a cat	10.6 (1.3, 85.8)	40.0 (33.1, 46.9)	93.2 (89.6, 96.7)	13.3 (8.6, 18.1)	98.3 (96.5, 100.0)
Tx1	Vertigo	16.9 (1.2, 34.6)	85.7 (80.8, 90.6)	61.2 (54.3, 68.0)	7.6 (3.9, 11.3)	99.1 (97.8, 100.0)
Tx2	Natural water contact: cultivating rice	2.9 (1.3, 6.4)	30.3 (23.8, 36.7)	85.7 (80.8, 90.6)	57.5 (50.6, 64.4)	65.8 (59.2, 72.5)
	Drinking water: fountain	0.4 (0.2, 0.9)	30.3 (23.8, 36.7)	52.1 (45.1, 59.1)	28.8 (22.4, 35.1)	53.9 (46.9, 60.1)
	Using soap for washing clothes	0.1 (0.02, 0.6)	89.5 (85.2, 93.8)	1.7 (0.1, 3.5)	36.8 (30.0, 43.5)	20.0 (14.4, 25.6)
	Washing hands when returning from work	0.5 (0.2, 0.9)	25.0 (18.9, 31.1)	53.8 (46.8, 60.8)	25.7 (19.5, 31.8)	52.9 (45.9, 59.9)
	Worm infections considered frequent in household	4.4 (1.4, 14.1)	18.4 (13.0, 23.9)	95.0 (91.9, 98.0)	70.0 (63.6, 76.4)	64.6 (57.9, 71.3)
Tx3	Natural water contact: cultivating rice	2.8 (1.3, 6.2)	29.6 (23.2, 36.0)	86.0 (81.1, 90.8)	60.0 (53.1, 66.9)	63.2 (56.5, 70.0)
	Drinking water: fountain	0.4 (0.2, 0.8)	30.9 (24.4, 37.4)	51.8 (44.7, 58.8)	31.3 (24.7, 37.8)	51.3 (44.3, 58.3)
	Using soap for washing clothes	0.1 (0.02, 0.8)	90.1 (85.9, 94.3)	1.8 (0.01, 3.6)	39.5 (32.6, 46.3)	20.0 (14.4, 25.6)
	Washing hands when returning from work	0.4 (0.2, 0.8)	24.7 (18.6, 30.7)	52.6 (45.6, 59.6)	27.0 (20.8, 33.3)	49.6 (42.6, 56.6)
	Worm infections considered frequent in household	5.4 (1.7, 17.9)	18.5 (13.1, 24.0)	95.6 (92.7, 98.5)	75.0 (68.9, 81.1)	62.3 (55.5, 69.1)

The study was carried out in June 2010 in the Taabo health demographic surveillance system, south-central Côte d'Ivoire. Stepwise backward elimination was performed, removing explanatory variables with the highest p-value one at the time, as long as the Akaike information criterion (AIC) decreased. Diagnostic indicators for each risk factor, sign, and symptom are indicated. Tx1 = treatment group 1 (i.e., praziquantel against schistosomiasis). Tx2 = treatment group 2 (i.e., benzimidazole against soil-transmitted helminthiasis). Tx3 = treatment group 3 (i.e., praziquantel and benzimidazole against schistosomiasis and soil-transmitted helminthiasis, respectively). CI = confidence interval.

10.4.5. Diagnostic properties of risk factors, signs, and symptoms

If each of the significant risk factors, signs, and symptoms revealed from the multivariable analysis was considered as diagnostic variable on its own, estimated sensitivity and specificity showed that at least one of the two diagnostic indicators was ≤50% with the exception of vertigo and belonging to Tx1 (sensitivity = 85.7%, 95% CI: 80.8-90.6%; specificity = 61.2%, 95% CI: 54.3-68.0%) (Table 36). However, when calculating the respective specificity for vertigo as a diagnostic indicator for Tx1, a high number of false-positives was masked by the high number of correctly identified negatives in the studied low schistosomiasis prevalence sample, as revealed by the inferior corresponding PPV of 7.6% (95% CI: 3.9-11.3%).

When considering the combined score, the only combinations that achieved values >50% for sensitivity, specificity, and the predictive values occurred for Tx2 and Tx3 at the cut-off level >1 (Table 37). By increasing the cut-off levels for predicting positive cases, the number of false-positives decreased and the number of false-negatives increased, consequentially leading to lower sensitivities and higher specificities.

Table 37. Diagnostic properties of a combined score at different cut-off levels in the diagnosis of helminth infections and treatment groups.

Parasite or treatment group	Combined score cut-off levels for predicting positive cases	Number of predicted positive cases	Sensitivity in % (95% CI)	Specificity in % (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
S. mansoni	>0	13	50.0 (43.0, 57.0)	94.2 (91.0, 97.5)	15.4 (10.3, 20.5)	98.9 (97.4, 100.0)
Hookworm	>0	142	86.7 (81.9, 91.4)	35.8 (29.1, 42.6)	45.8 (38.8, 52.8)	81.1 (75.6, 86.6)
	>1	36	33.3 (26.7, 40.0)	90.8 (86.8, 94.9)	69.4 (63.0, 75.9)	68.6 (62.0, 75.1)
	>2	7	9.3 (5.3, 13.4)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	63.8 (57.1, 70.6)
	>3	0	NA	NA	NA	NA
T. trichiura	>0	23	60.0 (53.1, 66.9)	89.5 (85.2, 93.8)	13.0 (8.3, 17.8)	98.8 (97.3, 100.0)
	>1	1	20.0 (14.4, 25.6)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	97.9 (95.9, 99.9)
Tx1	>0	79	85.7 (80.8, 90.6)	61.2 (54.3, 68.0)	7.6 (3.9, 11.3)	99.1 (97.8, 100.0)
Tx2	>0	168	97.4 (95.1, 99.6)	21.0 (15.3, 26.7)	44.1 (37.1, 51.0)	92.6 (88.9, 96.3)
	>1	108	75.0 (68.9, 81.1)	57.1 (50.2, 64.1)	52.8 (45.8, 59.8)	78.2 (72.4, 84.0)
	>2	25	25.0 (18.9, 31.1)	95.0 (91.9, 98.0)	76.0 (70.0, 82.0)	66.5 (59.8, 73.1)
	>3	5	6.6 (3.1, 10.1)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	62.6 (55.8, 69.4)
	>4	0	NA	NA	NA	NA
Tx3	>0	168	96.3 (93.7, 99.0)	21.1 (15.3, 26.8)	46.4 (39.4, 53.4)	88.9 (84.5, 93.3)
	>1	108	75.3 (69.3, 81.4)	58.8 (51.9, 65.7)	56.5 (49.5, 63.4)	77.0 (71.1, 82.9)
	>2	25	24.7 (18.6, 30.7)	95.6 (92.7, 98.5)	80.0 (74.4, 85.6)	64.1 (57.4, 70.9)
	>3	5	6.2 (2.8, 9.6)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	60.0 (53.1, 66.9)
	>4	0	NA	NA	NA	NA

The study was carried out in June 2010 in the Taabo health demographic surveillance system, south-central Côte d'Ivoire. Significance ($p < 0.05$) of associations between risk factors, signs, and symptoms and parasites and treatment groups, respectively, was previously determined with multivariable logistic regression modeling, including a stepwise backward elimination. Participant's combined score was obtained by coding all significantly associated risk factors, signs, and symptoms as 0 or 1with the higher score indicating elevated odds for being infected with the respective helminth or belonging to a certain treatment group. The scores from all significantly associated risk factors, signs, and symptoms were then summed up to obtain each participant's combined score. Tx1 = treatment group 1 (i.e., praziquantel against schistosomiasis). Tx2 = treatment group 2 (i.e., benzimidazole against soil-transmitted helminthiasis). Tx3 = treatment group 3 (i.e., praziquantel and benzimidazole against schistosomiasis and soil-transmitted helminthiasis, respectively). CI = confidence interval. NA = not applicable as all individuals predicted as negative at the respective cut-off level.

10.5. Discussion

In the present study, we juxtaposed quality-controlled parasitological data pertaining to schistosome and soil-transmitted helminth infections to socio-demographic data and detailed information on risk factors, signs, and symptoms. Data were obtained during a cross-sectional epidemiological survey conducted in mid-2010 in the Taabo HDSS in south-central Côte d'Ivoire. The intention of this study was twofold. First, we wanted to inform the local health authorities in the study area about risk factors, signs, and symptoms associated with schistosomiasis and soil-transmitted helminthiasis. Second, we were interested in the performance of an anamnestic questionnaire to predict helminth infection in an area subjected to preventive chemotherapy and a strengthened health system. Our study area might therefore represent a typical setting of low-endemicity helminthiasis due to sustained control interventions. Disappointingly, not a single risk factor, sign, or symptom, or combinations of them, revealed promising statistical associations and diagnostic properties in this 'new parasitic landscape' of control-induced low endemicity.

Nevertheless, some issues warrant further discussion. First, the sample size of our study was relatively small (n = 195 adults with complete parasitological and questionnaire data) and, with the exception of hookworm infection (39%), helminth prevalences were indeed very low (<5%). The heads of households and, if possible, a second adult household member of the opposite sex were purposefully sampled from over 1,100 participants who were enrolled during the cross-sectional epidemiological survey in the Taabo HDSS. Importantly, the prevalences of helminth infections in the cross-sectional epidemiological survey were similar to those in our study sample. In the overall survey, the prevalence of hookworm, *S. haematobium*, *S. mansoni*, *T. trichiura*, and *A. lumbricoides* were 31.3%, 3.7%, 2.1%, 1.6%, and 0.8%, respectively (E. K. N'Goran and colleagues, unpublished results).

Second, the low prevalence and intensity of helminth infection are the likely result of recent control efforts (i.e., annual deworming, health education, improved sanitation, and strengthened health system), which turned the previously polyparasitic study area into an area, where mainly hookworm infections remain. Indeed, N'Goran and colleagues reported a *S. haematobium* prevalence among school children in selected villages of 70% and above in the early and mid-1990s, and still in 2001,[32,33,43] whereas surveys conducted in 2008 and 2009 prior to Taabo HDSS-related deworming activities and other control interventions revealed hookworm prevalences of 51-89%.[34,35] We can expect similar helminth prevalences in other communities where preventive chemotherapy campaigns are underway. The relative

importance of hookworm *versus* the roundworm *A. lumbricoides* will likely be higher now as single-dose albendazole has a considerably lower efficacy in eliminating hookworm compared to *A. lumbricoides* infection.[44] For example, a recent study in Yunnan province, People's Republic of China demonstrated a 67.1% prevalence of hookworm prior to single-dose albendazole, and a prevalence of 20.7% 3-4 weeks after treatment. In the same study, the prevalence of *A. lumbricoides* dropped from 95.1% to 3.7%.[45] With the scale up of preventive chemotherapy against helminthiases, it is likely that hookworm (and *T. trichiura*) infections will predominate in areas which were once highly endemic for schistosomiasis and soil-transmitted helminthiasis. Although our study area can now be considered a low endemicity region for schistosomiasis and a moderate endemicity area for soil-transmitted helminthiasis,[29] it is a consequence of local helminth control efforts, and might therefore differ to other naturally occurring low or moderate endemic settings.

Third, as efforts are underway to integrate different control programs targeting multiple neglected tropical diseases,[46,47] questions arise as to how one might identify treatment-specific groups most efficiently. Hence, we did not only consider helminth-specific groups, but also treatment-specific groups. This is in line with recent WHO policies, which state that ''preventive chemotherapy interventions should be conceived as drug-based rather than disease-based: emphasis should be on the best, coordinated use of the available drugs rather than on specific forms of helminthiasis''.[18] However, due to the low prevalence *Schistosoma* infection, our praziquantel treatment group (Tx1) also became comparatively small and due to the several fold higher prevalence of hookworm infection, our benzimidazole treatment group (Tx2), and our combined treatment group (Tx3) were clearly driven by the hookworm cases. Therefore, it is difficult to draw firm conclusions and further verification is needed to assess whether anamnestic questionnaires targeting at specific treatment groups may constitute a potential way forward in settings with higher levels of helminth co-endemicity. Also of note when further following a treatment group design, there are other intestinal parasites such as *Strongyloides stercoralis*,[34,35,48,49] which should be included in future considerations, and their rapid assessment and treatment within treatment groups of existing, efficacious, safe, often donated, or low-cost drug combinations[50,51] may further enhance the usefulness of the approach.

Fourth, people reporting that worm infections are frequent in their household when directly asked showed higher odds of hookworm infection, and hence they were more likely to belong to two of the treatment groups considered here (Tx2 and Tx3). People may have some knowledge about helminth infections, possibly acquired during previous research and

interventions in the region. If this hypothesis could be confirmed in future studies, the local control efforts should implicitly draw on this knowledge.[52]

Fifth, we applied comparatively simple statistical models to analyze the data, including univariable and multivariable models and a scoring method, which is similar to approaches frequently applied in other health-related tests.[53-56] Interestingly, an approach using a scoring method and associated flexible score thresholds to predict positive cases may allow for the adaptation of the questionnaire's sensitivity, specificity, and predictive values. However, better methods to elicit potentially useful anamnestic questions and their optimal combination would be needed.

Sixth, our anamnestic questionnaire did not perform well for predicting schistosomiasis and soil-transmitted helminth infections in the Taabo HDSS area where control interventions against helminthiases, other neglected tropical diseases, and malaria are underway. The lack of a clear and readily assessable epidemiological and clinical footprint in control-induced low-endemicity settings makes it difficult to inform local health workers and village authorities about the disease and to motivate them to keep up the disease control efforts. Such difficulties are inherent to control-induced low-endemicity settings and have also been noted on the ''last mile'' of dracunculiasis eradication.[57] Adapting a surveillance-response mechanism (i.e., surveillance for detection of new cases, followed by setting-specific health intervention in response to the cases picked up in the surveillance) should be considered as the way forward.

In conclusion, we recommend further studies in the Taabo HDSS, but also in other areas with currently still higher prevalences and intensities of helminth infections, to shed additional light on the scope and limits of anamnestic questionnaires as monitoring and guidance tool for neglected tropical disease control programs. Certainly, other clinical factors such as physical exam features and rapid diagnostic tests should be further evaluated as well. Likewise, improvements of alternative helminth diagnostics should be kept in mind in order to continuously appraise the optimal combination of the different diagnostic and monitoring tools. For instance, the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE; http://score.uga.edu) conducted a multi-country study to assess the diagnostic accuracy of a commercially available point-of-care urine circulating cathodic antigen (POC-CCA) assay for the rapid detection of *S. mansoni* infection, which showed that POC-CCA urine tests are more sensitive than routine Kato-Katz thick smears.[58] Combining features of the different diagnostic and monitoring tools in consideration of the setting-specific levels of endemicity of the different parasites will become more important as prevalence rates and

infection intensities decline due to successful morbidity and infection control and such combinations will likely result in the most efficient care at the point-of-contact. Of note, the European research network NIDIAG is currently aiming at the development of improved, simple, integrated, and cost-effective diagnosis and treatment algorithms for clinical syndromes related to neglected tropical diseases (NIDIAG; http://www.nidiag.org) and such more comprehensive approaches may also provide the necessary framework for the additional evaluation and potential application of anamnestic questionnaires.

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11. Discussion

The main purpose of this PhD thesis was to develop, validate, and apply tools for assessing the morbidity and burden caused by different neglected tropical diseases (NTDs) at different geographical scales. This overarching goal was subdivided into the three main objectives:

(i) to assess the global burden of food-borne trematodiasis in terms of DALYs;

(ii) to develop, validate, and apply tools for the assessment of the average disability incurred by an individual infected with schistosomes and/or soil-transmitted helminths; and

(iii) to further explore the potential of anamnestic questionnaire tools for guiding schistosomiasis and soil-transmitted helminthiasis control efforts.

As indicated in the overarching goal, the thesis adhered to the strategic nexus of Swiss TPH, which emphasizes the cycle of innovation, validation, and application of tools, approaches and strategies in public health (Table 38). Consequently, the following discussion focuses on each of the three main objectives and their potential progression from innovation to validation and application.

Table 38. Contribution of the different chapters of the present PhD thesis to the strategic nexus of Swiss TPH.

CHAPTER	INNOVATION	VALIDATION	APPLICATION
5			The current knowledge about the manifestation, diagnosis, and management of food-borne trematodiasis was reviewed
6	For the first time, the global burden of food-borne trematodiasis was assessed in terms of DALYs and pressing research needs identified		
7	The effect of schistosomiasis and soil-transmitted helminthiasis on children's physical fitness was investigated with shuttle run tests		
8		Results of a quality of life questionnaire pertaining to children's physical fitness were compared to objectively measured physical fitness and implications for the exploration of the putative impact of helminth infections discussed	
9	The effect of schistosomiasis and soil-transmitted helminthiasis on adults' quality of life was investigated with a quality of life questionnaire		
10	The potential for further refinements of existing anamnestic questionnaires for schistosomiasis and soil-transmitted helminthiasis was explored in a pilot study		

The strategic nexus of the Swiss TPH emphasizes the continuum of innovation, validation and application of tools, approaches and strategies in public health. DALYs = disability-adjusted life years.

11.1. Assessing the global burden of food-borne trematodiasis

Based on a systematic review, we summarized the current knowledge about the manifestation, diagnosis and management of food-borne trematodiasis in a clinical review (Chapter 5).[1] We then used this knowledge to assess – for the first time – the global burden of food-borne trematodiasis in terms of DALYs (Chapter 6).[2] We find that, in 2005, an estimated 56.2 million people were infected with food-borne trematodes worldwide, 7.9 million suffered from severe sequelae and 7,158 died mainly due to cholangiocarcinoma (caused by *Clonorchis sinensis* and *Opisthorchis viverrini*) and cerebral infection (caused by *Paragonimus* spp.). These figures result in a global burden of 665,352 DALYs for the year 2005.[2]

Considerable simplifications are revealed in our disease models used for the burden estimation, when they are compared with the natural history as described in the clinical review.[1,2] This divergence mainly reflects the gap between qualitative statements based on biomedical observations and the availability of reliable quantitative population level data. For instance, it is widely accepted that liver fluke infections induce cholangiocarcinoma,[3,4] even though the exact mechanism of the carcinogenesis remains to be determined.[5-8] Cholangiocarcinoma is one of the most fatal cancers[9] and estimates of attributable deaths were as high as 28,000 in 2004 for Thailand alone.[10] However, the crucial question for assessing the burden of food-borne trematodiasis is how many of these cholangiocarcinoma cases are due to food-borne trematode infections. For our global burden estimates, we had to rely on just five studies, which reported on the odds ratio between *C. sinensis* infections and cholangiocarcinoma, and three studies, which reported on the odds ratio between *O. viverrini* infections and cholangiocarcinoma.[2] Based on these odds ratios, we calculated that 1,323 people died due to *O. viverrini*-induced cholangiocarcinoma throughout Southeast Asia in 2005, for instance.[2] These figures implicate that far less than every 20th death due to cholangiocarcinoma is caused by liver flukes in Thailand, which we, as well as others, consider as a conservative estimate.[2,10]

A second shortcoming of our burden estimates has been revealed in a recently finalized manuscript. By simply juxtaposing countries which were included in our global burden estimates to all countries with reported autochthonous cases of human food-borne trematodes infections, we demonstrated that many countries were not considered in our burden estimates due to missing reliable prevalence data on the national level.[11]

Despite these shortcomings, we and others consider our global burden estimates as a valuable benchmark and stimulus for future investigations.[2,10] In order to further improve and validate our estimates, the frequency and progression of signs and symptoms attributable to food-borne trematode infections as listed in Table 7 should be quantified to unravel the disease models from simple egg count dependency. Furthermore, if not yet existing, disability weights have to be assigned to well-defined signs and symptoms (see also Chapter 11.2). First efforts to determine disability weights due to clonorchiasis have been made recently and resulted in a summary disability weight of 0.075 for all infection intensities.[12] For comparison, we used disability weights of 0.104, but only for the 8.2% of all cases modeled as heavy infections in our burden estimate (Appendix 13.2.5.).[2] Hence, by applying this newly established disability weight (~3/4 of the disability weight currently used in our model) on all infected instead of only those 8% modeled with heavy infections, the YLD part of the clonorchiasis burden estimates would roughly increase by a factor 9. As a result, our estimates for the total global burden due to *C. sinensis* infections would more than double and result in over half a million DALYs for clonorchiasis alone.

Regarding the many countries, which report cases of food-borne trematodiasis but are not included in the presented burden estimates, emphasis should be placed on the realization of additional, carefully designed national surveys. Often, information is missing at the very basic, i.e., individual and local level, leading to 'guesstimates' at the national level and global summary measures, which have to be interpreted very carefully. Optimally, new national surveys would trigger local studies, which in turn rely on individual level data and avoid frequent problems such as "preferential sampling".[13] Reliable individual, local, national and global morbidity and mortality information would be most useful for decision making and the design of control efforts at each of the respective levels. Hence, morbidity and mortality assessments have their justification at all geographical scales and different scales should be seen as complementary rather than exclusionary to each other. However, as simple as this sounds as far away are we currently from achieving such optimal information in many countries.

Of note, advanced modeling approaches are in the end only as good as the quality and quantity of the underlying localized data points permit. For instance, with regard to spatial modeling approaches of food-borne trematodiasis, it is noteworthy that transmission may involve an even stronger behavioral component as schistosomiasis or soil-transmitted helminthiasis due to the implicit need for the consumption of undercooked, mainly aquatic products. However, compared to spatially explicit environmental indicators, such behavioral

covariates are more complex to obtain and include in spatial models and this ambiguity about human behavior may seriously complicate the prediction of human infections.[14]

In the current global burden of diseases study, DisMod 3 is used to compute disease specific, internally consistent and complete sets of the five epidemiological key indicators prevalence, incidence, remission, mortality and duration. As initial input, the software needs a minimum of three of these indicators. To the best of my knowledge, DisMod 3 draws then on pre-programmed large-scale demographic background data (e.g., age and sex distributions and life tables), but allows only for the interpolation of estimates by world regions (see Chapters 6 and 13) or – probably with some additional configurations – by countries.[15] In order to become an even more useful tool, future DisMod versions should include options to upload additional, smaller scale demographic background data in combination with associated epidemiological key indicators and to interpolate these information also at local levels.

Realizing the importance of well-designed national surveys, WHO's Food-borne Disease Burden Epidemiology Reference Group (FERG) initiated efforts to strengthen the capacity of countries to undertake such surveys and also supported local pilot studies.[16] Additional good examples should set precedents for increasingly bridging not only the work at different geographical scales, but also the gap between basic burden research and urgently needed practical control efforts. Thereby, the objection that DALYs and burden of disease studies are not worth the bother and only withdraw scarce resources from more urgently needed practical public health interventions[17] could be invalidated. Nevertheless, it is important to keep in mind that burden of disease assessments need considerable resources during their innovation and validation phase and only if the results are turned into action, they may provide real benefits by assisting in the most efficient (re-)allocation of scarce resources and the actual reduction of human suffering.

An immediate application of our own global burden of food-borne trematodiasis assessment is the more prominent placement of this widely neglected infectious disease cluster on the radar screen of organizations, donors and scientists. Next logical applications include costing and cost- effectiveness studies to further assess the potential of food-borne trematodiasis control programs. For instance, according to often used WHO criteria, interventions are considered as highly cost-effective if the incremental cost-effectiveness ratio (ICER) per DALY averted is less than the per capita gross domestic product (GDP) and as still cost-effective if the ICER per DALY averted is below three times the per capita GDP.[18] Such criteria could be used to calculate thresholds at which interventions are still cost-effective and to evaluate different scenarios of food-borne trematodiasis control.

Of particular interest with regard to such health economic evaluations, first, the burden due to food-borne trematodiasis is highly aggregated in some endemic areas (e.g., *O. viverrini* infections in northern and eastern Thailand and neighboring Lao PDR[19]). Hence, even though the respective burden estimates may not reach the most alarming levels of other conditions at the global scale, they may constitute an important public health problem in endemic areas and consequentially represent a cost-effective target for control in these regions. The "First WHO Report on Neglected Tropical Diseases" may provide good benchmarks for estimated number of DALYs, economic costs and costs per DALY averted of other NTDs, stratified by WHO regions.[20] Second, cost estimates for lost wages and medical care due to opisthorchiasis and cholangiocarcinoma in Thailand have been substantial, totaling US$ 85-120 million annually.[21,22] Third, besides the costs on human health, food-borne trematodes also negatively impact on livestock and aquaculture production. For example, the annual economic loss in livestock production due to fascioliasis has been estimated at US$ 50 million in Peru.[23] Fourth, the potential for piggybacking on, and integration with other helminth control programs, has hardly been exploited,[24] even though integrated approaches have recently been shown to be successful in many countries.[25,26] However, additional reflections about novel, multi-disease, and intersectoral approaches to harness the respective synergies have been initiated.[27] Fifth, the repeated call for more integrated and intersectoral approaches instead of only preventive chemotherapy may become unmistakable with regard to clonorchiasis and opisthorchiasis as first indications point towards an increased risk for cholangiocarcinoma among people who were repeatedly treated and re-infected with these liver flukes (Peter Odermatt, personal communication). This last point underscores the need for continued monitoring of implemented interventions and the associated effects on the targeted disease burden.[20]

11.2. Generating evidence on disability due to schistosomiasis and soil-transmitted helminthiasis

In order to generate new, patient-based evidence on the disability incurred by individuals infected with schistosomes and soil-transmitted helminths, we conducted cross-sectional surveys with schoolchildren and adults in Côte d'Ivoire. We could not identify any effect of schistosomiasis and soil-transmitted helminthiasis on children's physical fitness as objectively measured in a maximal multistage 20 m shuttle run test (Chapter 7)[28] and as self-reported in a questionnaire, which was based on a quality of life questionnaire pertaining to physical fitness

(Chapter 8).[29] However, we found statistically significant correlations between objectively measured and self-reported physical fitness. We therefore concluded that the quality of life questionnaire proofed valid to assess children's physical fitness, which is promising for the more general use of quality of life questionnaires (Chapter 8).[29] Finally, we could indeed identify significant negative effects of *S. mansoni* and *T. trichiura* infections on adults' quality of life as self-reported in such questionnaires (Chapter 9).[30]

Potential explanations for the rather unexpected findings that schistosomiasis and soil-transmitted helminthiasis had no effect on children's physical fitness, but negatively impacted adults' quality of life were already discussed in the respective chapters. However, three points are worth highlighting. First, in our initial study, it is conceivable that we excluded exactly those children from the physical fitness test due to medical concerns who suffered the most from their parasitic infections. At least, these children could be included in the questionnaire survey, but supposedly due to relative small sample sizes even their inclusion led to no significant difference.[28,29] Second, children are at highest risk of helminth infections, but most severe complications may only occur after years of advanced chronic infection and therefore in adolescents and adults (Chapter 1). This peculiarity may explain why we could identify an effect in adults, but not in children. Third, all our studies were cross-sectional surveys, which is probably not the optimal study design.

As mentioned in Chapter 1.7.3, the initial disability weights applied in burden estimates were solely based on expert opinion. It is only in the past years that more systematic and field-supported epidemiological surveys to assess the disability incurred by individuals suffering from certain conditions gained increased attention. Hence, most efforts – and particularly those targeted at NTDs such as ours – are still in rather early innovation and validation stages.[31-33] Particularly with regard to disability assessments due to parasitic helminths, it is important to note that infections may take years to resolve without treatment, that super-infections and re-infections are likely in endemic communities, and that the worms cause a diversity of contemporaneous pathology and disability during active infection, but also irreversible chronic morbidity, which may persist even after parasite clearance.[31] Nevertheless, based on the WHO's definition that health is a "state of complete physical, mental, and societal well-being and not merely the absence of disease or infirmity",[34] every deviation from this ideal, which is attributable to a certain condition, should be measured. Hence, innovative, systematic, and holistic approaches to more precisely assess and validate disability elicited by helminthiasis are essential.

Drawing from generic health-related quality of life concepts,[35-37] a potential conceptual framework for future studies may consider the four basic domains physical health, psychological health, social well-being and environmental quality (Figure 24). The first three domains may be uncontested, whereas the inclusion of an environmental domain (e.g., physical environment such as housing, pollution and noise, but also access to infrastructure and resources, safety and security) may be more controversial. However, besides being an important risk factor, the environment is also an important effect modifier of ill-health.[38,39] In addition, health-related quality of life questionnaires occasionally include also separate domains for pain, spirituality/religion and the level of independence (e.g., mobility, daily life activities, medical and non-medical substances).[35-37]

More systematic approaches may help to better define variables that should or should not be included in disability assessments and to better interpret results and identify knowledge gaps. For instance, Figure 24 indicates that our own work based on a maximal multistage 20 m shuttle run test (Chapters 7 and 8) provides mainly information on aerobic endurance, which is only one facet of physical fitness. Moreover, physical fitness is only one component of physical health and physical health is only one of four domains of health-related quality of life. Hence results from testing a single facet should not be over-interpreted. At the same time, Figure 24 may help to identify quality of life facets, which could be omitted as the respective condition under investigation may only marginally influence them, or facets which could be assessed simultaneously. For instance, there are different series of approximately 6-10 simple and quick tests, which are adaptable to all ages of participants and allow the assessment of physical fitness in all its facets.[40-44] Likewise, other test series are available or could be adapted/developed for other health-related quality of life domains (e.g., psychometric tests, cognitive tests, social network analysis, environmental assessments, etc.). As also indicated in Chapter 8, the combination of different test series and different methodologies (e.g., different tests to measure the same facet, more specific *vs*. more generic tools, mixed methods research) will provide exciting opportunities to further compare and validate tools as well as the resulting disability outcomes.

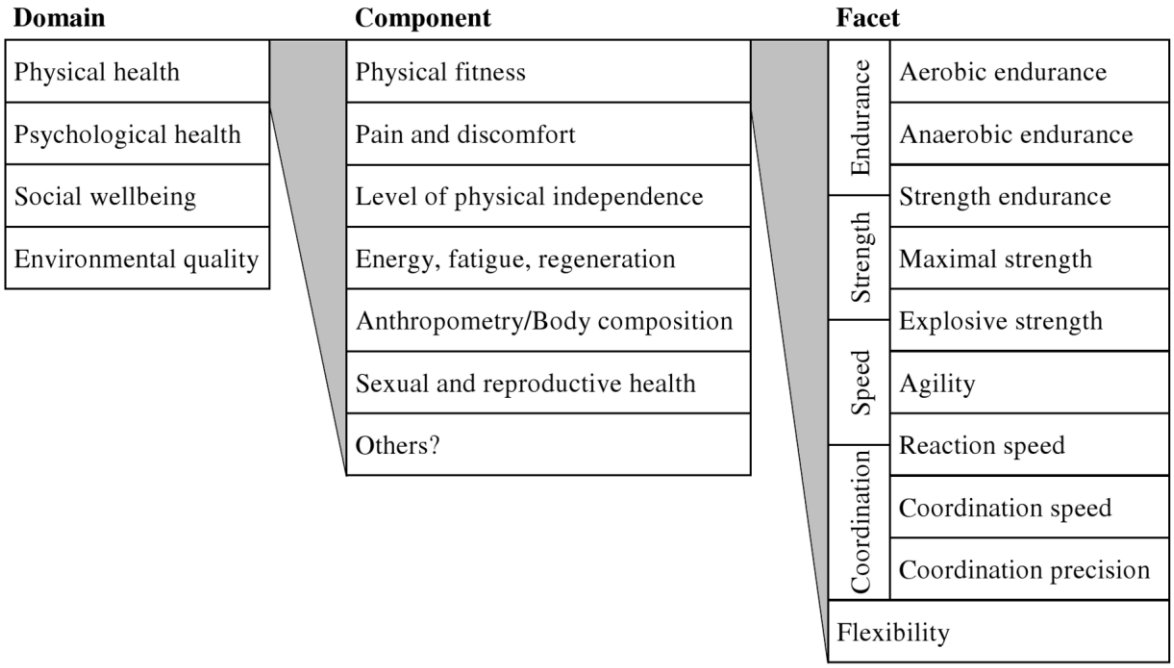

Figure 24. Proposed conceptual framework for future disability assessments based on individual health-related quality of life, exemplified for physical fitness. Individual health-related quality of life is primarily based on the four domains physical health, psychological health, social well-being and environmental quality. Each of these domains can be further sub-divided into different components and each component may be further sub-divided into different facets. This figure has been further developed based on references [35-37,40].

Optimally, future attempts to assess or validate disability rely on series of tests rather than a single test. The study design should be as rigorous as possible and particularly in case of treatment or other interventions carefully consider periods for remission, which may range from extremely short to endlessly long. In case of quickly curable, contemporaneous pathologies and disabilities (e.g., unadvanced, active helminth infections) randomised controlled trials should be feasible and set the standard. However, in case of slowly resolving chronic effects or even irreversible pathology and disability, randomised controlled trials may not be feasible and carefully designed case-control and longitudinal studies in the frame of long-term control programs may represent the best options. Irrespective of the detailed study design, special attention should also be paid to co-morbidity and age-specific effects.

Of note, first considerations have also been made about the assessment of the more indirect, societal (e.g., emotional, socio-economic) burden born by persons close to the directly affected and disabled individuals. However, while intuitively comprehensible, such an amendment would probably push the limits too far and constitute a hardly feasible task (e.g., the number of more or less severely affected persons may be highly variable not only between, but also within societies). Hence, it might be advisable to first improve the figures

on the direct burden before opening the Pandora's Box of indirect burden evaluation. As aforementioned, adhering to a more systematic conceptual framework for future disability assessments is essential for the clarification of what exactly should be reflected by the disability measurements. Questions such as what should be directly included and what are potentially important adjustments to consider (e.g., indirect, societal burden? environmental quality? local levels of poverty?) need to be answered.

The ultimate application of well-defined, revised disability measurements in burden estimates may correct important flaws of previous burden of disease studies and has the potential to markedly change the figures and deduced priority setting in public health. As indicated in Chapters 1 and 11, the global burden of schistosomiasis may rise from 1.7-4.5 million DALYs[45,46] to 70 million DALYs[32,47,48] and also the burden of clonorchiasis may more than double[2,12] just because of revised disability weights. Finally, and without further delving into the discussion about which burden measure may be best for future use, it is important to realize that both major types of health-adjusted life years (HALYs; measures that combine mortality and morbidity in a single measure), namely DALYs and quality-adjusted life years (QALYs), need an indicator to measure disability or – synonymously – health-related quality of life.[49]

11.3. Exploring anamnestic questionnaire tools for guiding schistosomiasis and soil-transmitted helminthiasis control

Realizing the need for reliable, simple, rapid, inexpensive and culturally adapted diagnostic methods for the guidance of schistosomiasis and soil-transmitted helminthiasis control at all levels of endemicity, we conducted a study in the Taabo HDSS, south-central Côte d'Ivoire, in mid-2010 (Chapter 10). The main objectives were to assess risk factors, signs and symptoms associated with the respective helminthic infections in a control-induced low-endemicity setting and to explore their potential in anamnestic rapid screening questionnaire tools. At first sight, we could not identify promising candidates among the considered risk factors, signs and symptoms in our pilot study. However, important issues, which future studies may wish to consider, were further discussed.

In order to further develop and validate the initial findings, a second study was carried out in the frame of the third annual parasitological survey and preventive chemotherapy campaign in the Taabo HDSS in summer 2011. This second study included 585 participants of all ages, who were subjected to parasitological diagnosis and a revised questionnaire. The

questionnaire included again questions on the individual and the household level as clustering of helminth infections in certain individuals[50-53] and households[54,55] may exist. Furthermore, individuals and households were again directly approached in order to circumvent low school enrolment and high school absenteeism, an admitted shortcoming of school-based questionnaires.[56-59] In-depth analyses of these data are still ongoing.

Importantly, future evaluations should not only carefully consider whom to ask, but also who asks. For instance, a well-accepted and fully integrated female anthropologist identified much higher numbers of miscarriages and stillbirths among nomadic women than an also very empathetic male clinician.[60] Similarly, during our own study, we made the observation that a woman reported no complaints when asked by a male clinician, but mentioned a swollen leg ("jambe enflée") when subsequently interviewed by one of the male field enumerators. Indeed, the woman was suffering from severe elephantiasis, most likely caused by lymphatic filariasis (Figure 25).

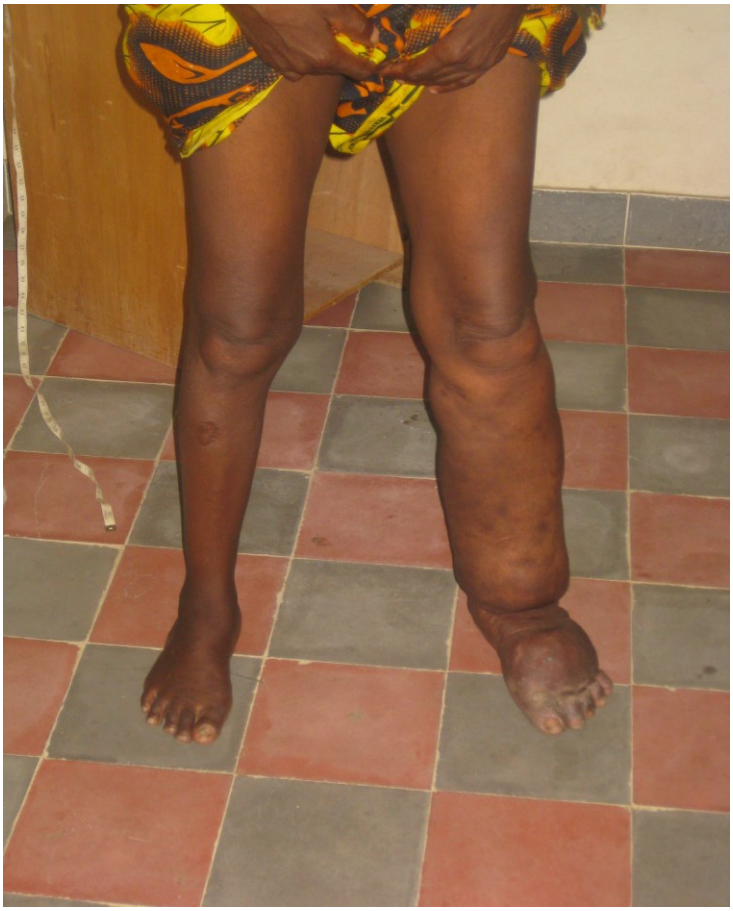

Figure 25. Female case of elephantiasis most likely caused by lymphatic filariasis. The case was observed during the survey carried out in June 2010 in the Taabo HDSS, south-central Côte d'Ivoire. The woman did not report any complaints when explicitly asked by a male clinician, but mentioned a swollen leg ("jambe enflée") when subsequently interviewed by one of the male field enumerators.

Besides anamnestic questionnaires, there are alternative and also constantly advanced approaches for the rapid screening of helminthic infections. Examples are the currently evaluated point-of-contact (POC) circulating cathiodic antigen (CCA) urine assays for *S. mansoni* infections,[61,62] but also lot quality assurance sampling (LQAS),[63] grid sampling[64] and spatial modeling,[65,66] which increasingly allow for guiding helminth control efforts even at smaller scale. These approaches should be continuously reviewed in order to identify potential synergies between the methods and to decide whether further efforts should be made in the development of anamnestic questionnaires or rather in the alternatives.

All aforementioned screening techniques are employed in the hope to better target control efforts, and hence to further improve the cost-effectiveness of interventions. For instance, a study from Uganda indicates that some rapid screening is superior to preventive chemotherapy in most settings because prevalence rates do not ubiquitously reach very high levels and treatment and delivery costs are still relevant.[63] Hence, current estimates that concurrent preventive chemotherapy against seven NTDs (including schistosomiasis and soil-transmitted helminthiasis) would cost US$ 0.40 per person per year and result in an economic rate of return of 15-30%[67] could even be surpassed. However, besides this purely economic argument, to end this thesis discussion, it should be re-emphasized that the control of NTDs contributes to at least five of the eight broader millennium development goals (MDGs). First, by tackling the intimate link between poverty and NTDs, removing infections helps to eradicate extreme poverty and hunger. Second, it helps reducing child morbidity and thereby supports primary education. Third, it directly helps to reduce child mortality. Fourth, it improves maternal health. Fifth, epidemiological evidence strongly suggests that it will improve the outcome of concurrent HIV/AIDS, malaria and tuberculosis and thereby also promote the fight against these “big three”.[68]

11.4. References

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12. Conclusion

Probably the most important finding of the most recent global burden of disease endeavor will be the renewed realization of how little is still known about the distribution and epidemiology of many diseases. This vagueness will be most pronounced for diseases, which primarily occur in developing countries (e.g., tropical diseases), but will also include diseases, which are very well documented in some countries, but not in others (e.g., cancer). However, besides the endless need for more and better data, more systematic concepts are imperative for future burden assessments. For instance, concepts have to clarify what disability weights – and therefore the resulting burden estimates – should exactly measure. Further clarification would help to prevent from exhausting, nebulous discussions.

As DALYs have become a frequently used measure to evaluate public health needs, it is of utmost importance to get the figures right and consider a complete list of conditions. Hence, we made an effort to assess, for the first time, the global burden of food-borne trematodiasis. Nevertheless, many other conditions are still missing (e.g., strongyloidiasis, taeniasis, toxoplasmosis, brucellosis).

Additionally, questions about the leadership, coordination, accessibility of data and transparency of methods of global burden of disease studies have to be addressed. To the best of my knowledge, WHO was partner in the latest global burden of disease endeavor, but – while welcoming all efforts pertaining to better knowledge – recently decided to not automatically endorse the results without further review because of the aforementioned organizational constraints. Clearly, as long as all these shortcomings exist, the global burden of disease study's initial objective to further decouple epidemiological assessments from advocacy will not be accomplished and advocacy will just reach a next, more abstract level instead.

With regard to individual morbidity and disability assessments, this PhD thesis tried to emphasize the importance of truly interdisciplinary work. The currently observable change of perspective from expert opinion towards field-based epidemiological survey data in the elicitation of disability weights may indeed correct some important flaws of previous burden of disease studies. To further support this highly welcome development, a potential way forward has been suggested in the discussion of this thesis.

At the current stage, it is too early to say anything about the potential of further refined anamnestic questionnaires to guide schistosomiasis and soil-transmitted helminthiasis control efforts. However, of note, if it may become possible to elicit effects of NTDs with carefully adapted and applied quality of life questionnaires, it is also conceivable that disease-

associated risk factors, signs and symptoms allow for the development of anamnestic questionnaires for rapid screening. Certainly, it will be no easy task, but the potential benefits warrant further efforts.

Finally, this thesis was governed by the idea that work on different geographical scales is complementary rather than exclusionary to each other and that basic research and practical control efforts should be as fruitfully combined as possible.

13. Appendix

13.1. Clinical review: manifestation, diagnosis and management of food-borne trematodiasis

13.1.1. Web reference list

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13.2. Global burden of human food-borne trematodiasis: a systematic review and meta-analysis

13.2.1. Webappendix 1. Table highlighting food-borne trematodes' taxonomy, human diseases caused and the respective source of transmission

Order	Family	Species	Fluke type	Disease	Transmission source
(Digenea)	Neodiplostomidae	*Fibricola cratera*	Intestinal fluke	Neodiplostomiasis	Food-borne: frog, snake
		Neodiplostomum seoulense	Intestinal fluke	Neodiplostomiasis	Food-borne: frog, snake, tadpole
Echinostomida	Cathaemaciidae	*Cathaemacia cabrerai*	Intestinal fluke	Echinostomiasis	Food-borne: unknown
	Echinostomatidae	*Acanthoparyphium tyosenense*	Intestinal fluke	Echinostomiasis	Food-borne: mussel, snail
		Artyfechinostomum malayanum	Intestinal fluke	Echinostomiasis	Food-borne: snail
		Artyfechinostomum oraoni	Intestinal fluke	Echinostomiasis	Food-borne: unknown
		Echinochasmus fujianensis	Intestinal fluke	Echinostomiasis	Food-borne: fish
		Echinochasmus japonicus	Intestinal fluke	Echinostomiasis	Food-borne: fish
		Echinochasmus jiufoensis	Intestinal fluke	Echinostomiasis	Food-borne: unknown
		Echinochasmus liliputanus	Intestinal fluke	Echinostomiasis	Food-borne: fish
		Echinochasmus perfoliatus	Intestinal fluke	Echinostomiasis	Food-borne: fish
		Echinoparyphium recurvatum	Intestinal fluke	Echinostomiasis	Food-borne: snail
		Echinostoma angustitestis	Intestinal fluke	Echinostomiasis	Food-borne: fish
		Echinostoma cinetorchis	Intestinal fluke	Echinostomiasis	Food-borne: fish, snail
		Echinostoma echinatum	Intestinal fluke	Echinostomiasis	Food-borne: mussel, snail
		Echinostoma hortense	Intestinal fluke	Echinostomiasis	Food-borne: fish
		Echinostoma ilocanum	Intestinal fluke	Echinostomiasis	Food-borne: snail
		Echinostoma macrorchis	Intestinal fluke	Echinostomiasis	Food-borne: snail
		Echinostoma malayanum	Intestinal fluke	Echinostomiasis	Food-borne: snail
		Echinostoma revolutum	Intestinal fluke	Echinostomiasis	Food-borne: mussel, snail
		Episthmium caninum	Intestinal fluke	Echinostomiasis	Food-borne: fish
		Himasthla muehlensi	Intestinal fluke	Echinostomiasis	Food-borne: mussel
		Hypoderaeum conoideum	Intestinal fluke	Echinostomiasis	Food-borne: snail
		Isthmiophora melis	Intestinal fluke	Echinostomiasis	Food-borne: tadpole
		Psilorchis hominis	Intestinal fluke	Echinostomiasis	Food-borne: unknown

The table is based on references [5-8] from the main text.

13.2.1. Webappendix 1. Continued

Order	Family	Species	Fluke type	Disease	Transmission source
Opisthorchiida	Fasciolidae	*Fasciola gigantica*	Liver fluke	Fascioliasis	Food-borne: plant, maybe water
		Fasciola hepatica	Liver fluke	Fascioliasis	Food-borne: plant, maybe water
		Fasciolopsis buski	Intestinal fluke	Fasciolopsiasis	Food-borne: plant
	Gastrodiscidae	*Gastrodiscoides hominis*	Intestinal fluke	Echinostomiasis	Food-borne: crab, frog, plant, tadpole
	Paramphistomidae	*Fischoederius elongatus*	Intestinal fluke	Echinostomiasis	Food-borne: plant
		Watsonius watsoni	Intestinal fluke	Echinostomiasis	Food-borne: plant
	Heterophyidae	*Apophallus donicus*	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Ascocotyle longa	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Centrocestus armatus	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Centrocestus caninus	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Centrocestus cuspidatus	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Centrocestus formosanus	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Centrocestus kurokawai	Intestinal fluke	Heterophyiasis	Food-borne: unknown
		Cryptocotyle lingue	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Haplorchis pleurolophocerca	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Haplorchis pumilio	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Haplorchis taichui	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Haplorchis vanissimus	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Haplorchis yokogawai	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Heterophyes dispar	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Heterophyes heterophyes	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Heterophyes nocens	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Heterophyopsis continua	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Metagonimus minutus	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Metagonimus miyatai	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Metagonimus takahashii	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Metagonimus yokogawai	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Procerovum calderoni	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Procerovum varium	Intestinal fluke	Heterophyiasis	Food-borne: unknown
		Pygidiopsis summa	Intestinal fluke	Heterophyiasis	Food-borne: fish

The table is based on references [5-8] from the main text.

13.2.1. Webappendix 1. Continued

Order	Family	Species	Fluke type	Disease	Transmission source
		Stellantchasmus falcatus	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Stellantchasmus formosanus	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Stellantchasmus pseudocirratus	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Stictodora fuscata	Intestinal fluke	Heterophyiasis	Food-borne: fish
		Stictodora lari	Intestinal fluke	Heterophyiasis	Food-borne: fish
	Opisthorchiidae	*Clonorchis sinensis*	Liver fluke	Clonorchiasis	Food-borne: fish
		Opisthorchis felineus	Liver fluke	Opisthorchiasis	Food-borne: fish
		Opisthorchis viverrini	Liver fluke	Opisthorchiasis	Food-borne: fish
Plagiorchiida	Dicrocoeliidae	*Dicrocoelium dendriticum*	Liver fluke	Dicrocoeliasis	Food-borne: ant
	Lecithodendriidae	*Phaneropsolus bonnei*	Intestinal fluke	Lecithodendriidiasis	Food-borne: fly, naiad of fly
		Phaneropsolus spinicirrus	Intestinal fluke	Lecithodendriidiasis	Food-borne: unknown
		Prosthodendrium molenkampi	Intestinal fluke	Lecithodendriidiasis	Food-borne: fly, naiad of fly
	Microphallidae	*Spelotrema brevicaeca*	Intestinal fluke	Microphallidiasis	Food-borne: crab, shrimp
	Nanophyetidae	*Nanophyetus salmincola*	Intestinal fluke	Nanophyetiasis	Food-borne: fish
	Paragonimidae	*Paragonimus africanus*	Lung fluke	Paragonimiasis	Food-borne: crab, shrimp, mammal meat
		Paragonimus heterotremus	Lung fluke	Paragonimiasis	Food-borne: crab, shrimp, mammal meat
		Paragonimus kellicotti	Lung fluke	Paragonimiasis	Food-borne: crab, shrimp, mammal meat
		Paragonimus mexicanus	Lung fluke	Paragonimiasis	Food-borne: crab, shrimp, mammal meat
		Paragonimus skrjabini	Lung fluke	Paragonimiasis	Food-borne: crab, shrimp, mammal meat
		Paragonimus uterobilateralis	Lung fluke	Paragonimiasis	Food-borne: crab, shrimp, mammal meat
		Paragonimus westermani	Lung fluke	Paragonimiasis	Food-borne: crab, shrimp, mammal meat
	Plagiorchiidae	*Plagiorchis harinasutai*	Intestinal fluke	Plagiochiasis	Food-borne: unknown
		Plagiorchis javensis	Intestinal fluke	Plagiochiasis	Food-borne: insect larva
		Plagiorchis muris	Intestinal fluke	Plagiochiasis	Food-borne: fish, insect, snail
		Plagiorchis philippinensis	Intestinal fluke	Plagiochiasis	Food-borne: insect larva
Strigeata	Brachylaimidae	*Brachylaima cribbi*	Intestinal fluke	Brachylaimiasis	Food-borne: snail
	Gymnophallidae	*Gymnophalloides seoi*	Intestinal fluke	Gymnophalloidiasis	Food-borne: mussel
Strigeatida	Strigeidae	*Cotylurus japonicus*	Intestinal fluke	Strigeidiasis	Food-borne: snail

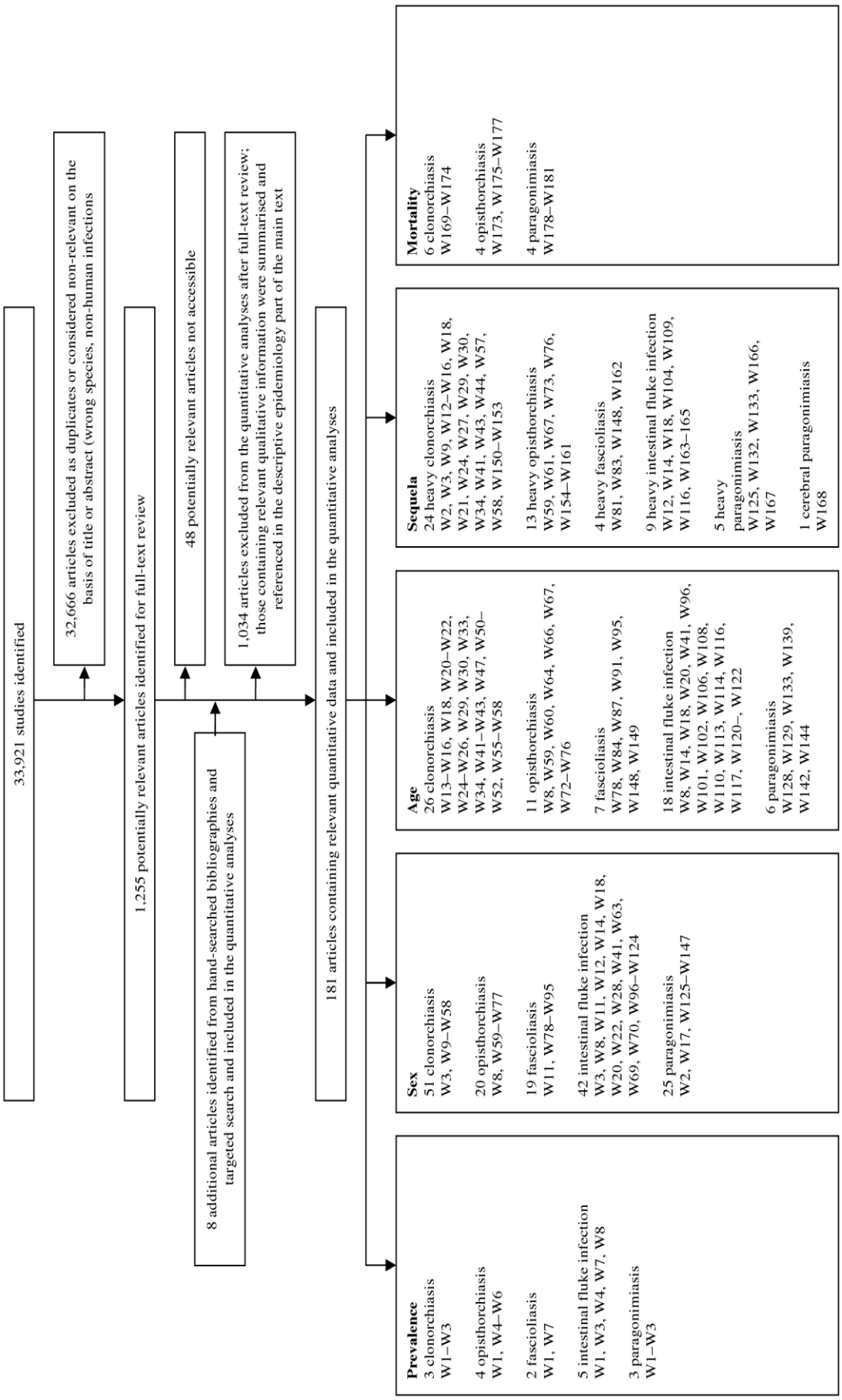
The table is based on references [5-8] from the main text.

13.2.2. Webappendix 2. Summary of the search strategy and selection criteria in our systematic review

Database	Thesaurus (Provider)	Search term ("or")	Inclusion ("and")	Exclusion ("not")	Number of hits
PubMed[a]	MeSH (US National Library of Medicine)	"trematode infections"	"humans"	"schistosomiasis"	2,884
		"food parasitology"	1980-2008	"schistosoma"	
WHO (WHOLIS)[a]	MeSH (US National Library of Medicine)	"trematode infections"	"humans"	"schistosomiasis"	14
		"food parasitology"	1980-2008	"schistosoma"	
FAO (FAOBIB)	AGROVOC (FAO)	"helminthoses"	1980-2008	"schistosomiasis"	410
		"food-borne diseases"		"nematode infections"	
EMBASE[a]	EMTREE (Elsevier)	"trematodiasis"	"humans"	"schistosomiasis"	613
		"food control AND parasitology"	1980-2008	"schistosoma"	
CAB Abstracts[a]	CAB Thesaurus (CABI)	"trematode infections"	"man"	"schistosomiasis"	3,353
		"food-borne diseases"	1980-2008	"schistosoma"	
LILACS	MeSH (US National Library of Medicine)	"trematode infections"	"humans"	"schistosomiasis"	26
		"food parasitology"	1980-2008	"schistosoma"	
ISI Web of Science	No thesaurus; normal keyword search	"trematod*", "food-borne", "plant-borne", "fish-borne", "fluke*", specific species and disease names[b]	"human*" 1980-2008	"schistosom*"	2,226
BIOSIS preview	No thesaurus; normal keyword search	"trematod*", "food-borne", "plant-borne", "fish-borne", "fluke*", specific species and disease names[b]	"human*" 1980-2008	"schistosom*"	9,069
Science Direct	No thesaurus; normal keyword search	"trematod*", "food-borne", "plant-borne", "fish-borne", "fluke*", specific species and disease names[b]	"human*" 1980-2008	"schistosom*"	14,838
African Journals Online	No thesaurus; normal keyword search	"trematod*", "food-borne", "plant-borne", "fish-borne", "fluke*", specific species and disease names[b]	1980-2008	---	354
SIGLE[a]	No thesaurus; normal keyword search	"trematod*", "food-borne", "plant-borne", "fish-borne", "fluke*", specific species and disease names[b]	1980-2008	---	134

The table highlights the databases searched, respective thesauruses, search terms, and Boolean operators used, and numbers of resulting hits. [a]Mandatory for the GBD 2010 study (see reference [1] from the main text). [b]See Appendix 13.2.1. *Wildcard, represents any group of characters, including no character.

13.2.3. Webappendix 3. Study selection



References containing solely qualitative information on food-borne trematodiasis are summarised and referenced in the main text. References containing quantitative datasets for the estimation of the global burden of food-borne trematodiasis are summarised and referenced here. Respective references are provided with a 'W' at the beginning to distinguish them from the other references given in the main text. Reference numbers W1-W181 correspond with the reference numbers given in Appendix 13.2.4.

13.2.4. Webappendix 4. Bibliographic details of references containing quantitative information for the global burden of food-borne trematodiasis estimation

Respective references are provided with a 'W' at the beginning to distinguish them from the other references given in the main text. Reference numbers W1-W181 correspond with the reference numbers given in Appendix 13.2.3.

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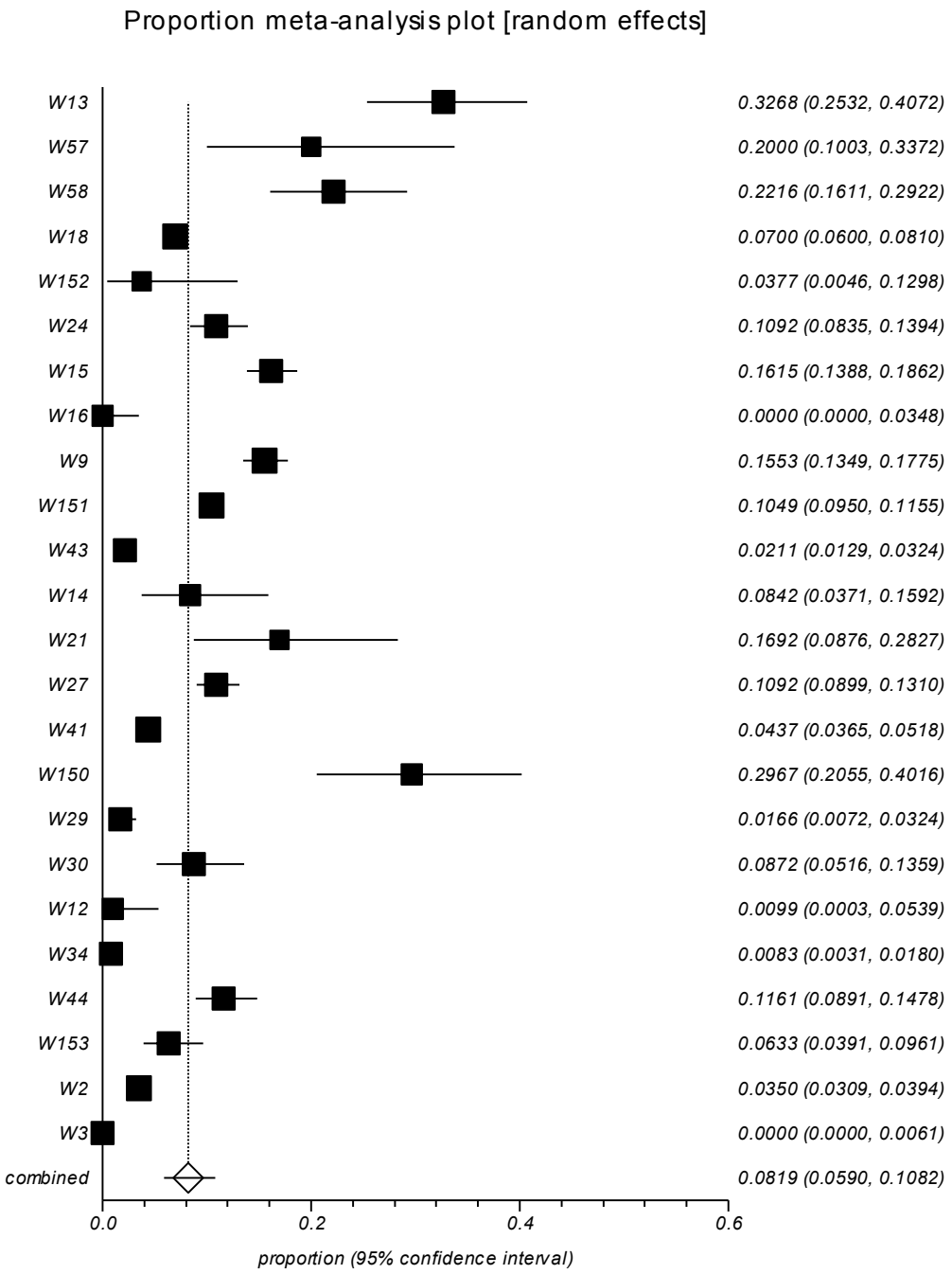
13.2.5. Webappendix 5. Forest plots of the meta-analysis on proportions of heavy food-borne trematode infections among all food-borne trematode infections

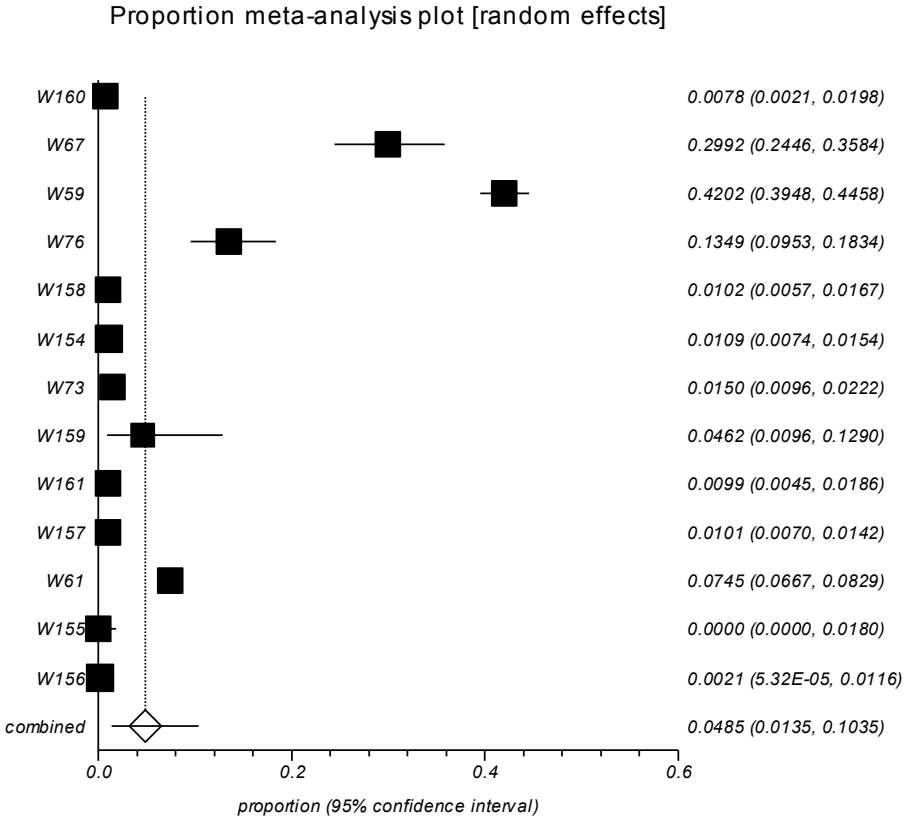
References are sorted according to the year of publication with newer ones closer to the bottom. Respective references are provided with a 'W' at the beginning to distinguish them from the other references given in the main text. Bibliographic details on the references of the quantitative datasets included are provided in Appendix 13.2.4.

Clonorchiasis

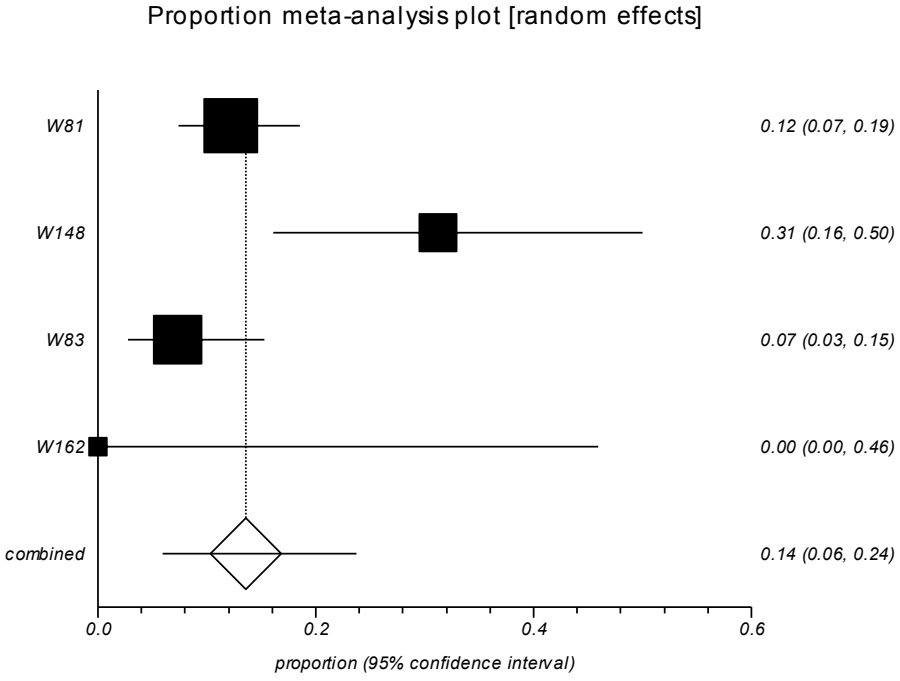


13.2.5. Webappendix 5. Continued

Opisthorchiasis

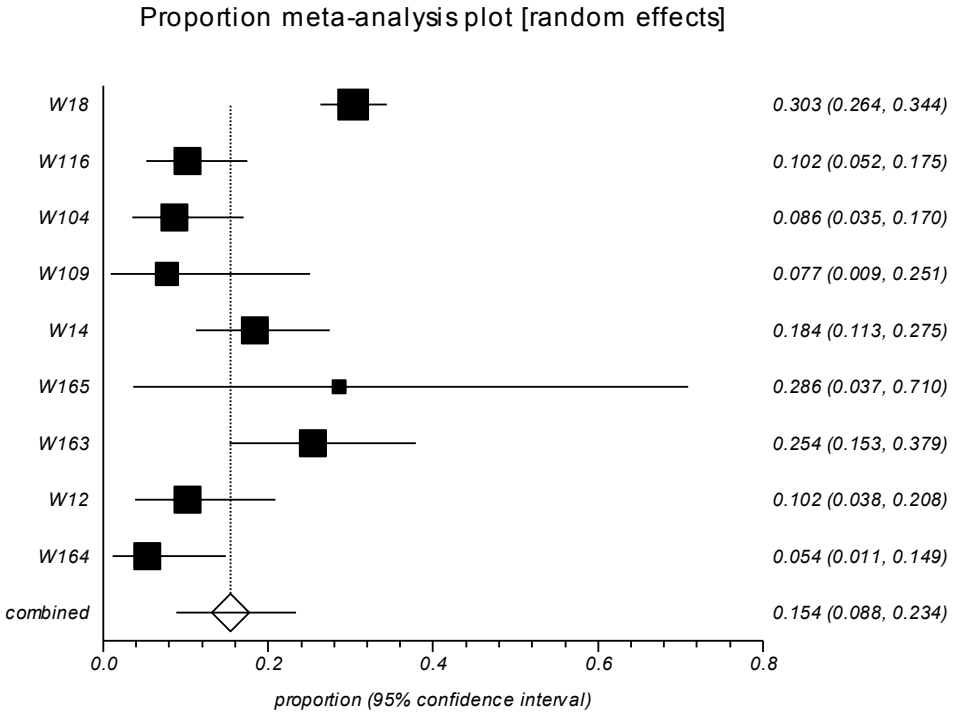


Fascioliasis

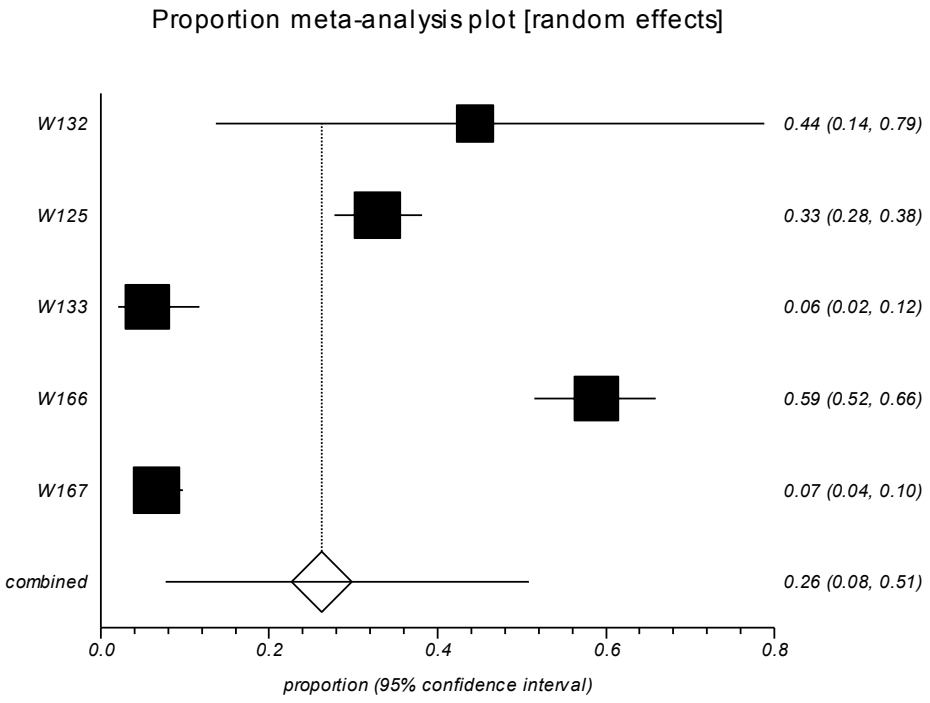


13.2.5. Webappendix 5. Continued

Intestinal fluke infections



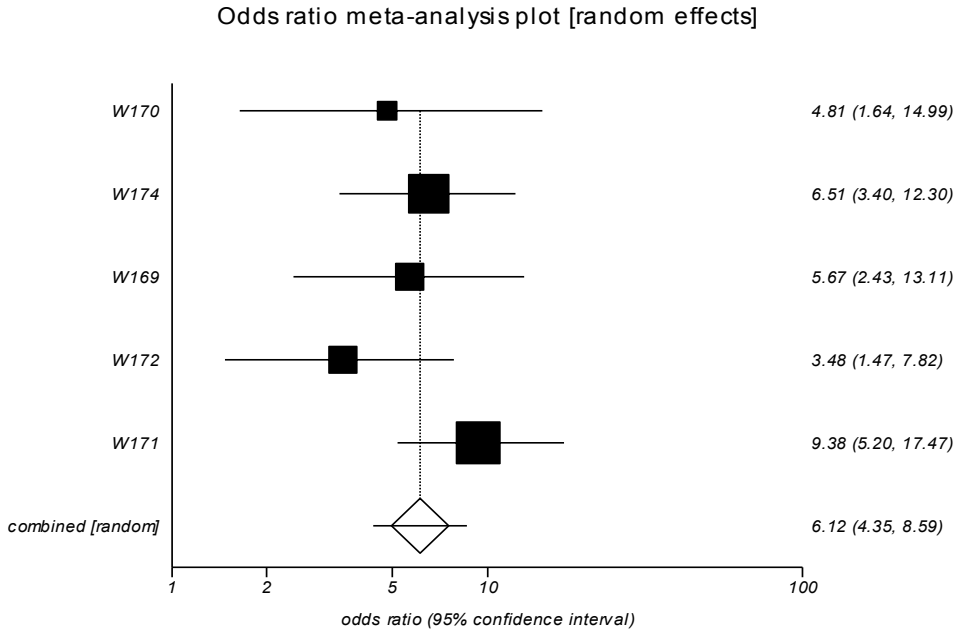
Paragonimiasis



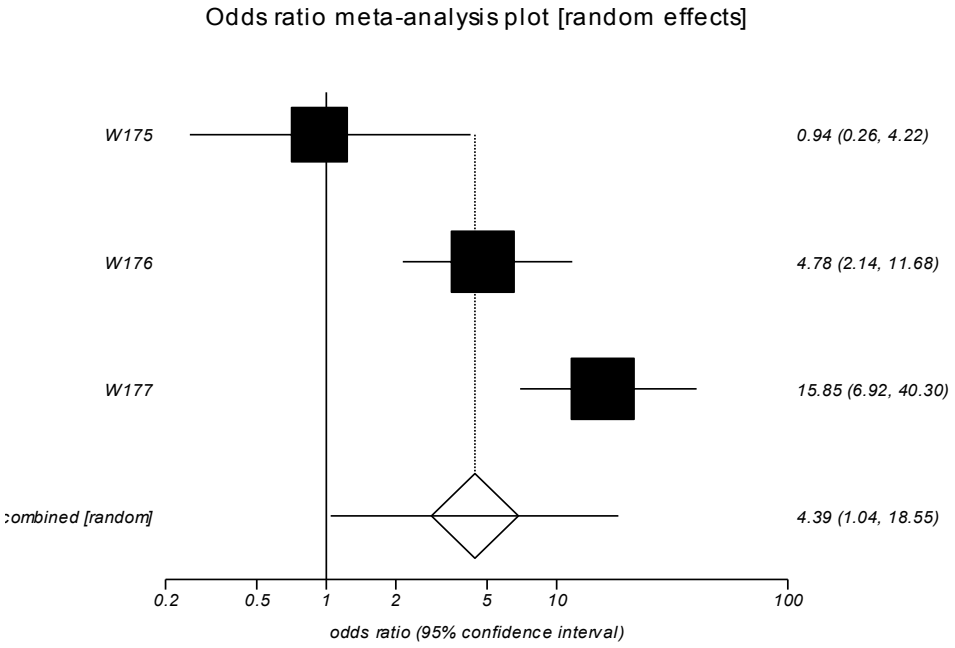
13.2.6. Webappendix 6. Forest plots of the meta-analysis on odds ratios between CCA and clonorchiasis and CCA and opisthorchiasis, respectively

References are sorted according to the year of publication with newer ones closer to the bottom. Respective references are provided with a 'W' at the beginning to distinguish them from the other references given in the main text. Bibliographic details on the references of the quantitative datasets included are provided in Appendix 13.2.4.

Clonorchiasis

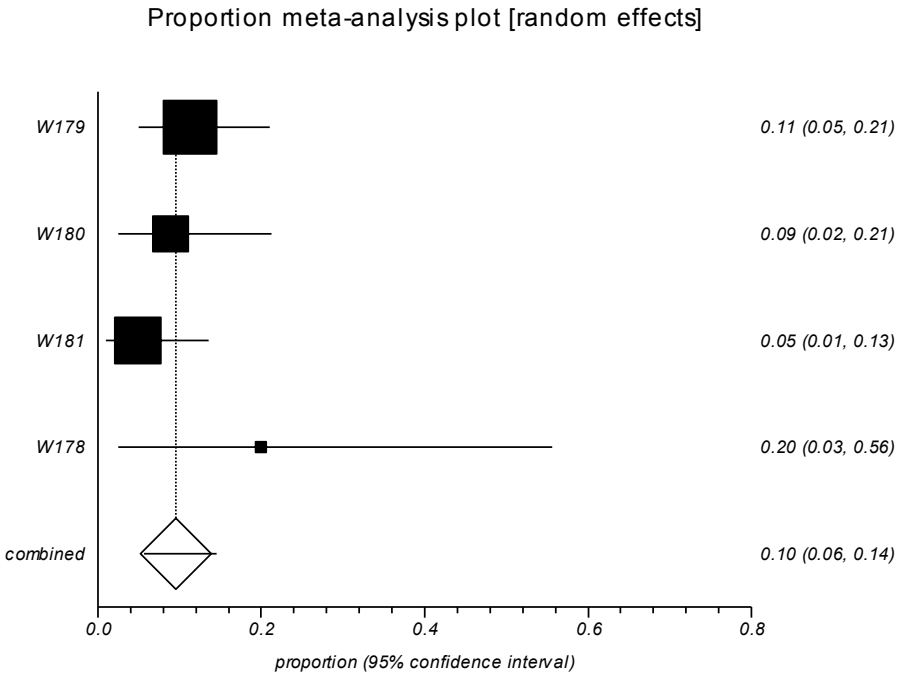


Opisthorchiasis



13.2.7. Webappendix 7. Forest plot of the meta-analysis on the proportions of cerebral paragonimiasis cases who die

References are sorted according to the year of publication with newer ones closer to the bottom. Respective references are provided with a 'W' at the beginning to distinguish them from the other references given in the main text. Bibliographic details on the references of the quantitative datasets included are provided in Appendix 13.2.4.

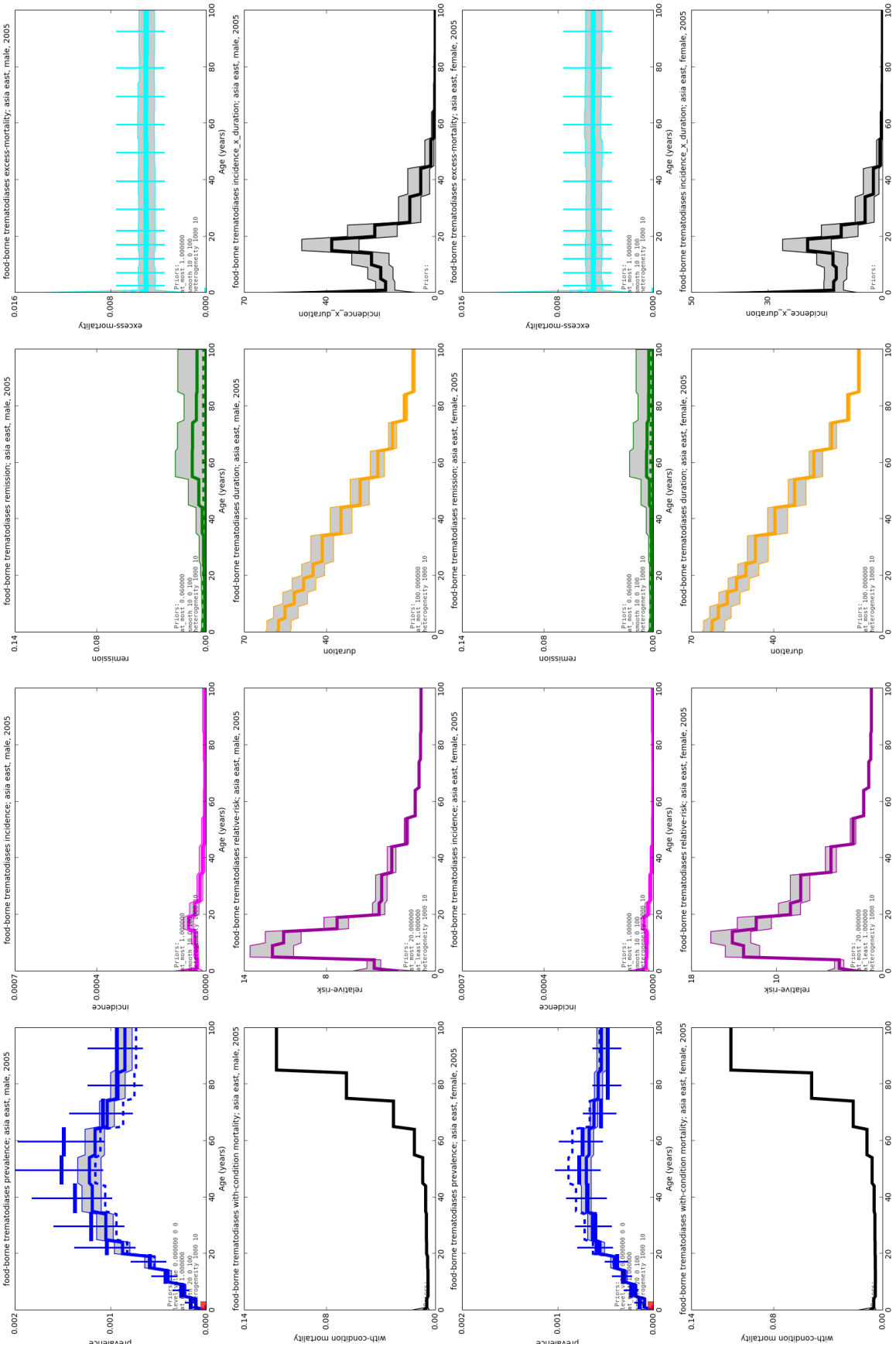


13.2.8. Webappendix 8. Parasite group-specific, region-specific, and sex-specific analytical graphs of the DisMod 3 outputs for the relevant sequelae

If provided, initial model input data are represented as unconnected horizontal lines for the respective age groups with vertical error bars. Final model output data are represented as continuous steplike lines at the respective ages with estimation errors displayed as surrounding gray-shaded areas. *Prevalence rates* are defined as number of people in the respective age group who had the condition at time t divided by the total number of people in the respective age group at time t. *Incidence rates* are defined as number of people in the respective age group who did not have the condition at time t-1 and got it before time t divided by the person years of people in the respective age group who did not have the condition during the period t-1 to t. *Remission rates* are defined as number of people in the respective age group who had the condition at time t-1 and remitted before time t divided by the person years of people in the respective age group who had the condition during the period t-1 to t. *Excess mortality rates* are defined as with condition mortality rates of people in the respective age group during the period t-1 to t minus without condition mortality rates of people in the respective age group during the period t-1 to t. *With condition mortality rates* are defined as number of people in the respective age group who had the condition at time t-1 and died before time t divided by person years of people in the respective age group who had the condition during the period t-1 to t. *Relative risks* are defined as with condition mortality rates of people in the respective age group during the period t-1 to t divided by without condition mortality rates of people in the respective age group during the period t-1 to t. *Durations* are defined as average time period in years until remission or death for someone who gets the disease at the respective age. *Incidence_x_duration* is defined as the product of these two variables, which is crucial for estimating the years lifed with disability.

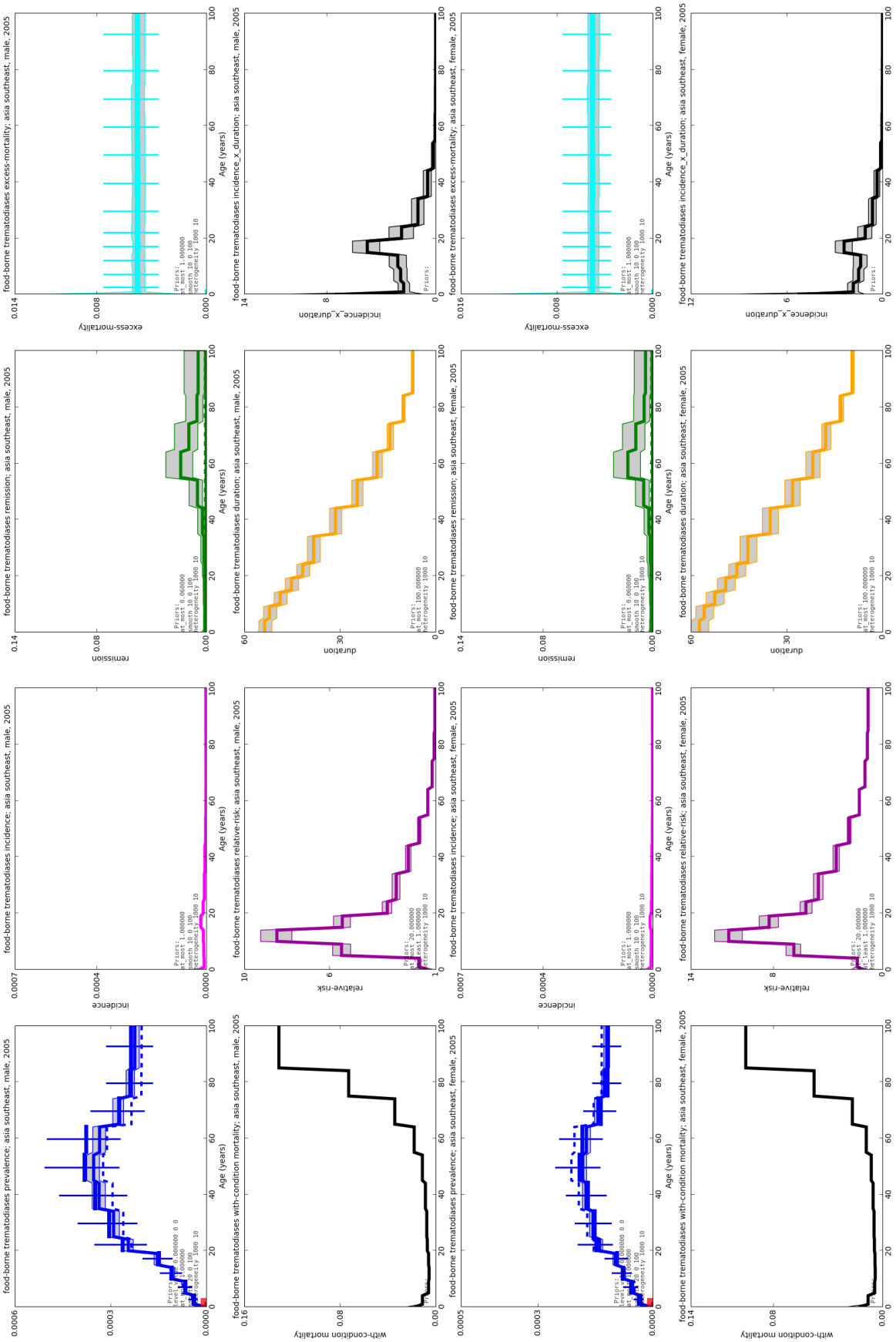
13.2.8. Webappendix 8. Continued

Heavy clonorchiasis: Asia, east



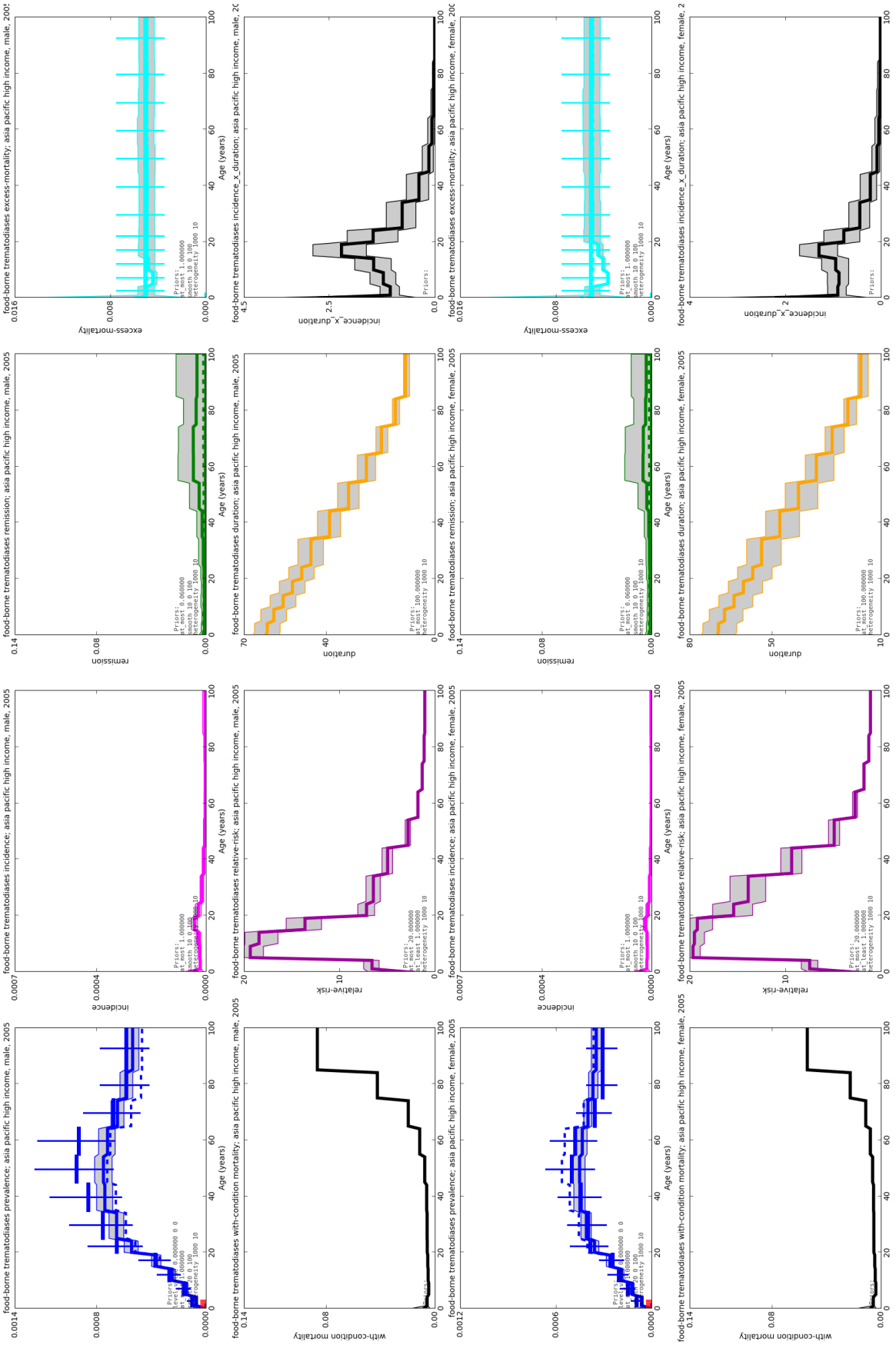
13.2.8. Webappendix 8. Continued

Heavy clonorchiasis: Asia, southeast



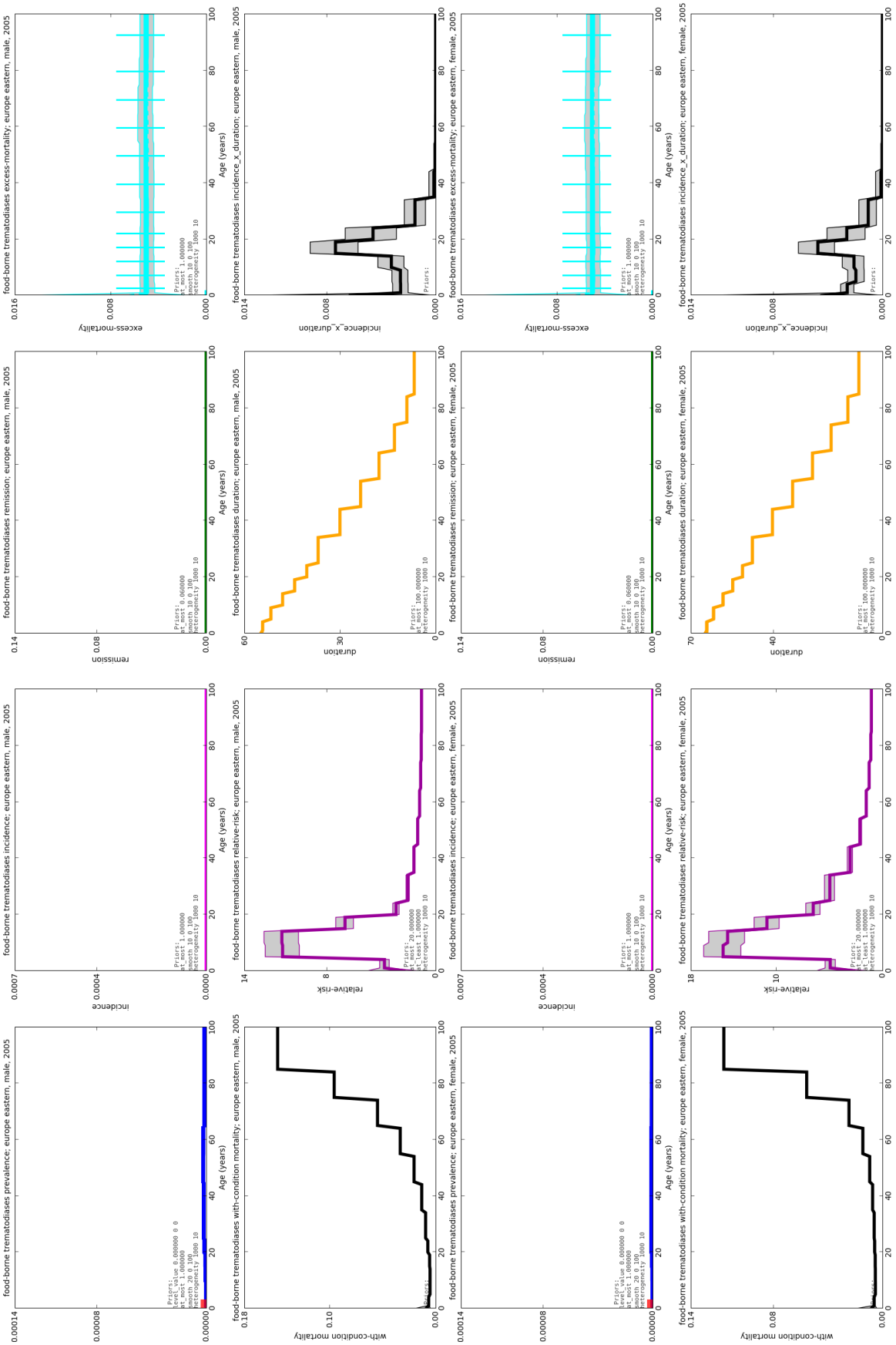
13.2.8. Webappendix 8. Continued

Heavy clonorchiasis: Asia Pacific, high income



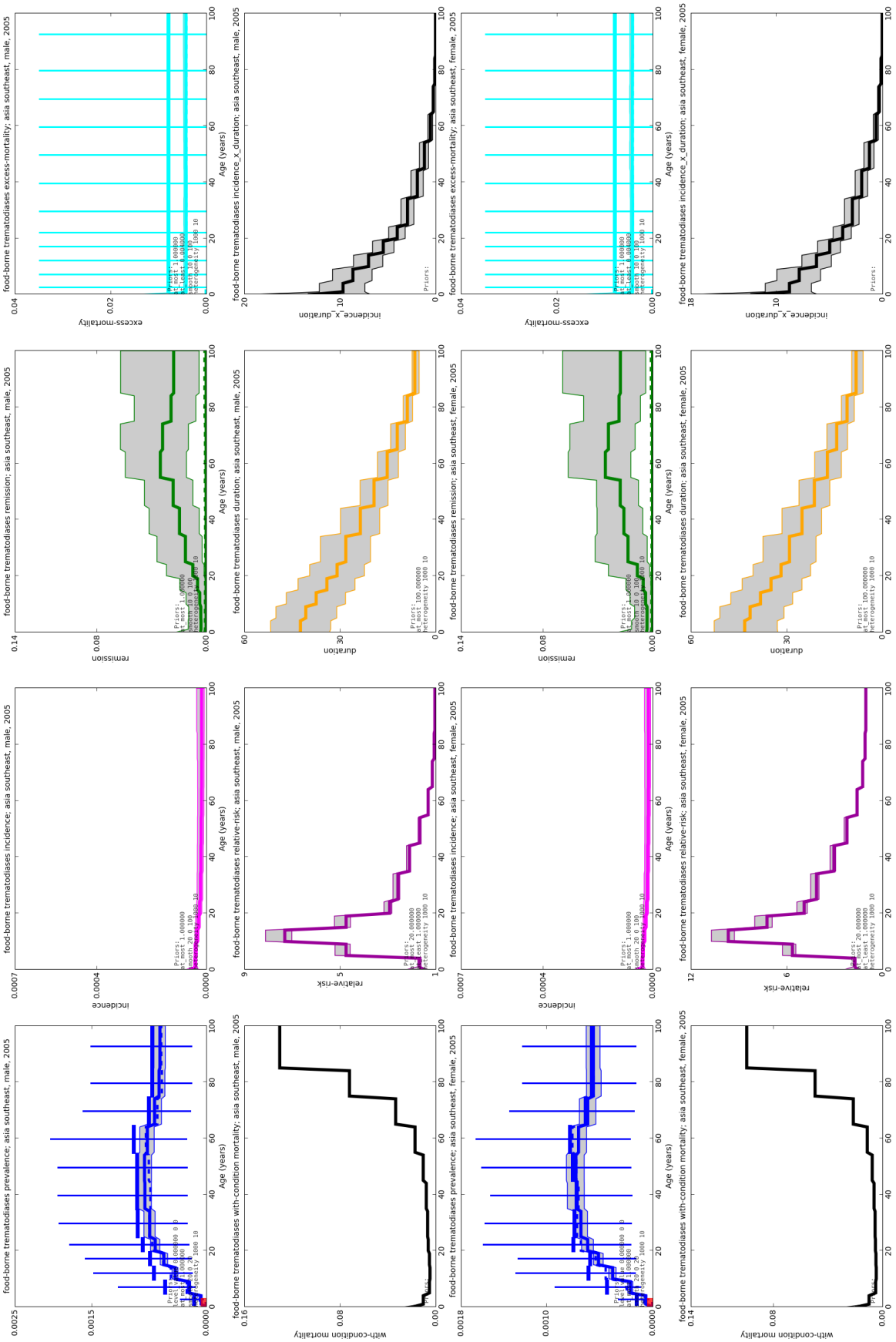
13.2.8. Webappendix 8. Continued

Heavy clonorchiasis: Europe, eastern



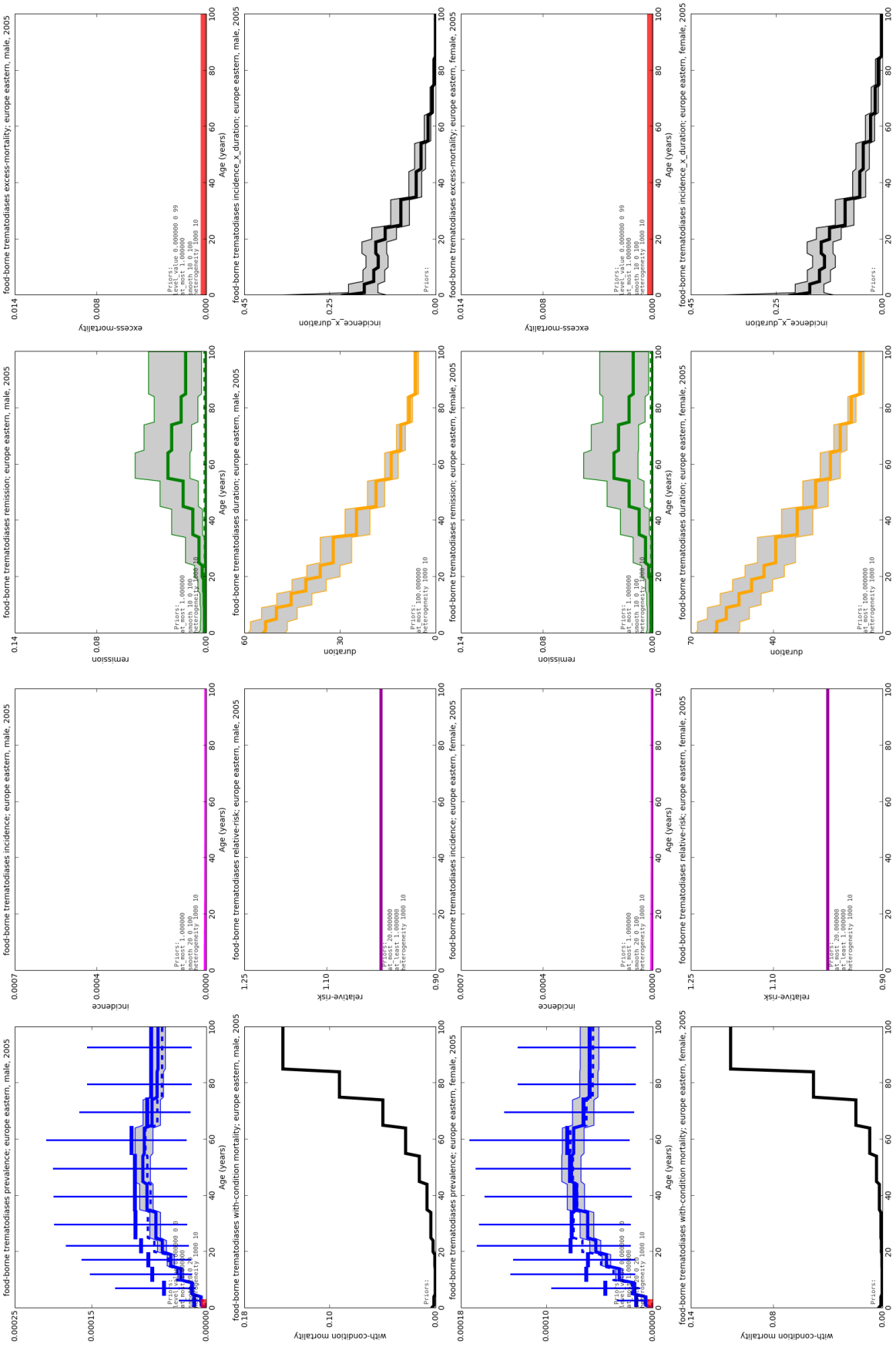
13.2.8. Webappendix 8. Continued

Heavy opisthorchiasis: Asia, southeast (*O. viverrini)*



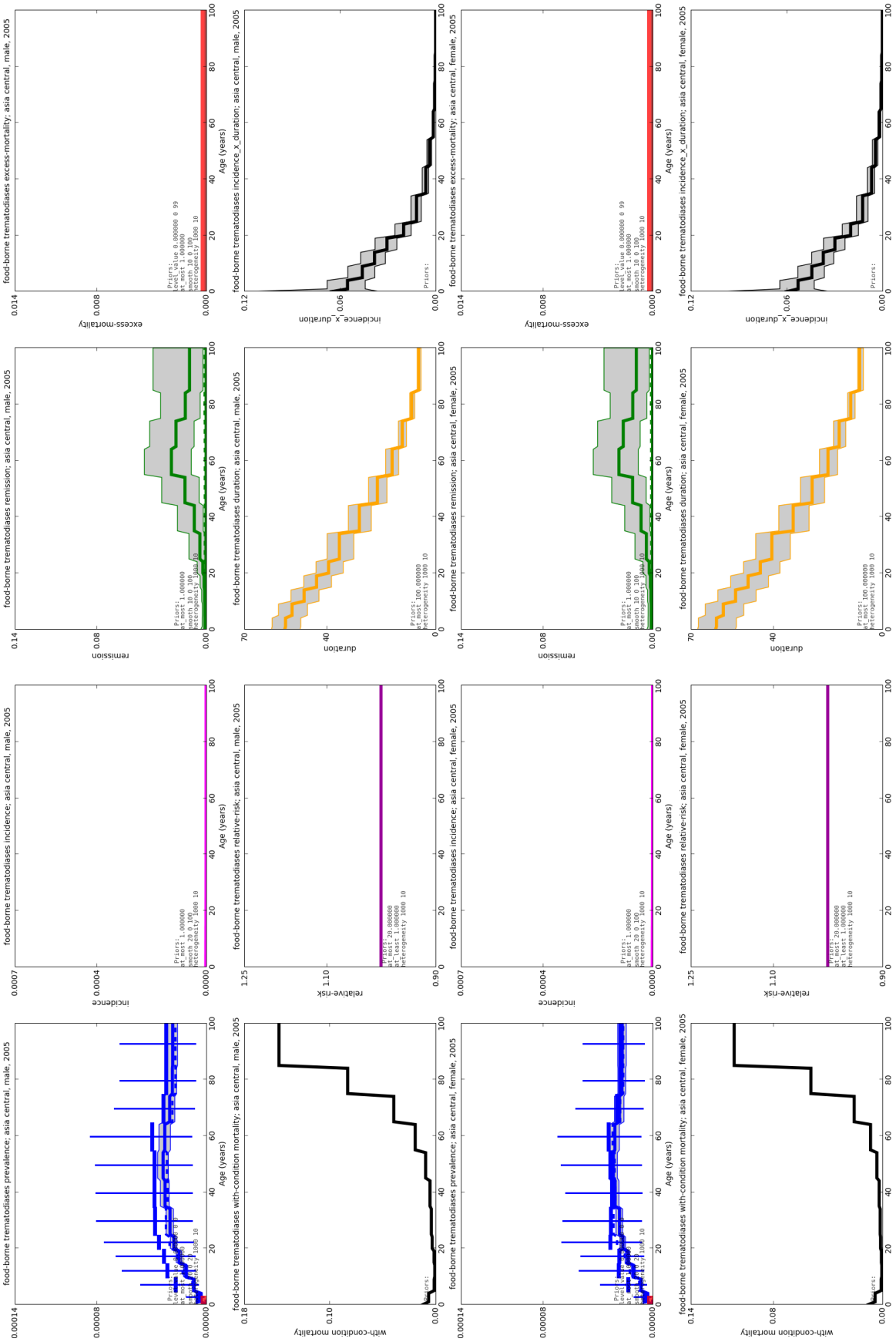
13.2.8. Webappendix 8. Continued

Heavy opisthorchiasis: Europe, eastern (*O. felineus)*



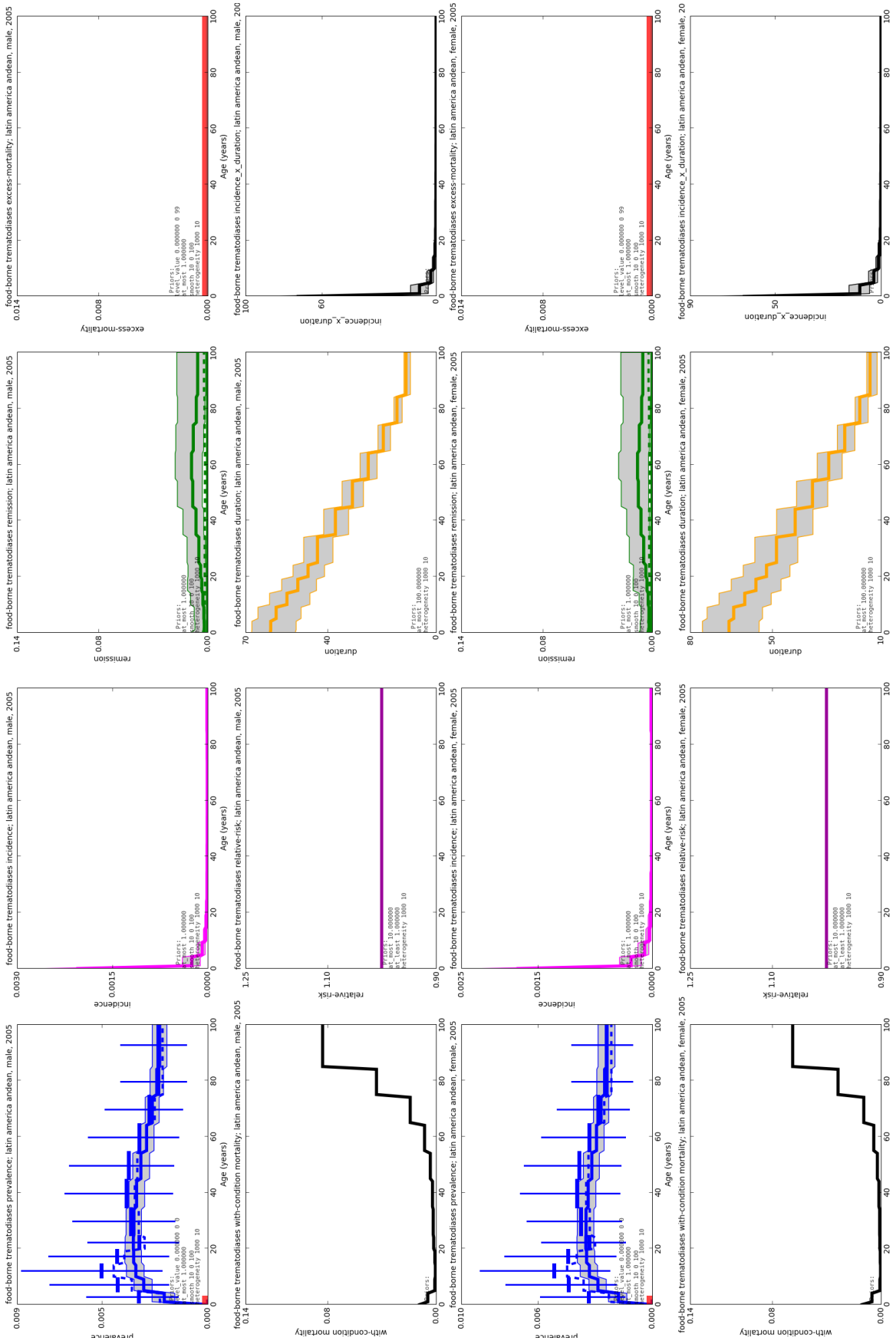
13.2.8. Webappendix 8. Continued

Heavy opisthorchiasis: Asia, central (*O. felineus)*



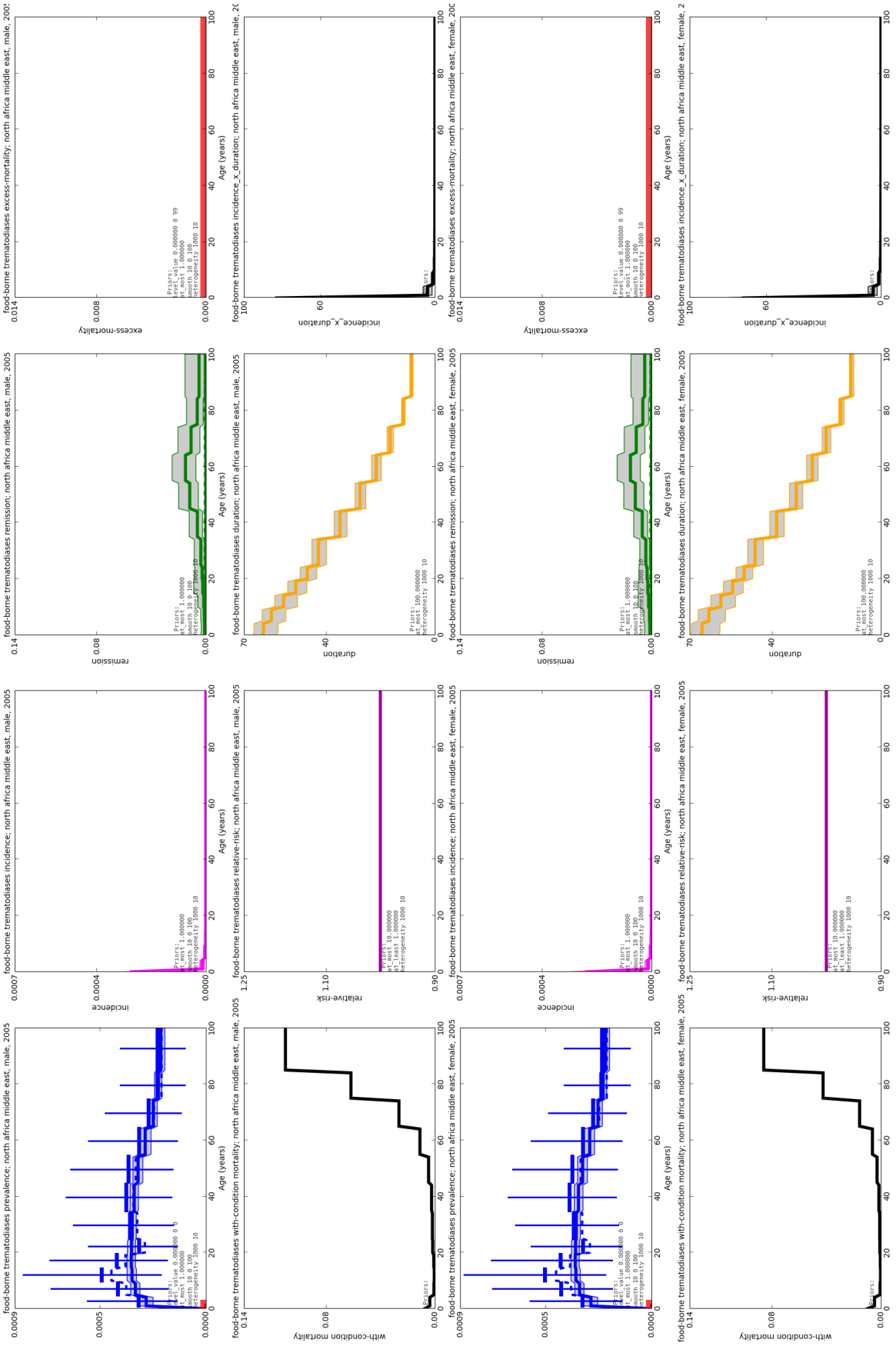
13.2.8. Webappendix 8. Continued

Heavy fasioliasis: Latin America, Andean



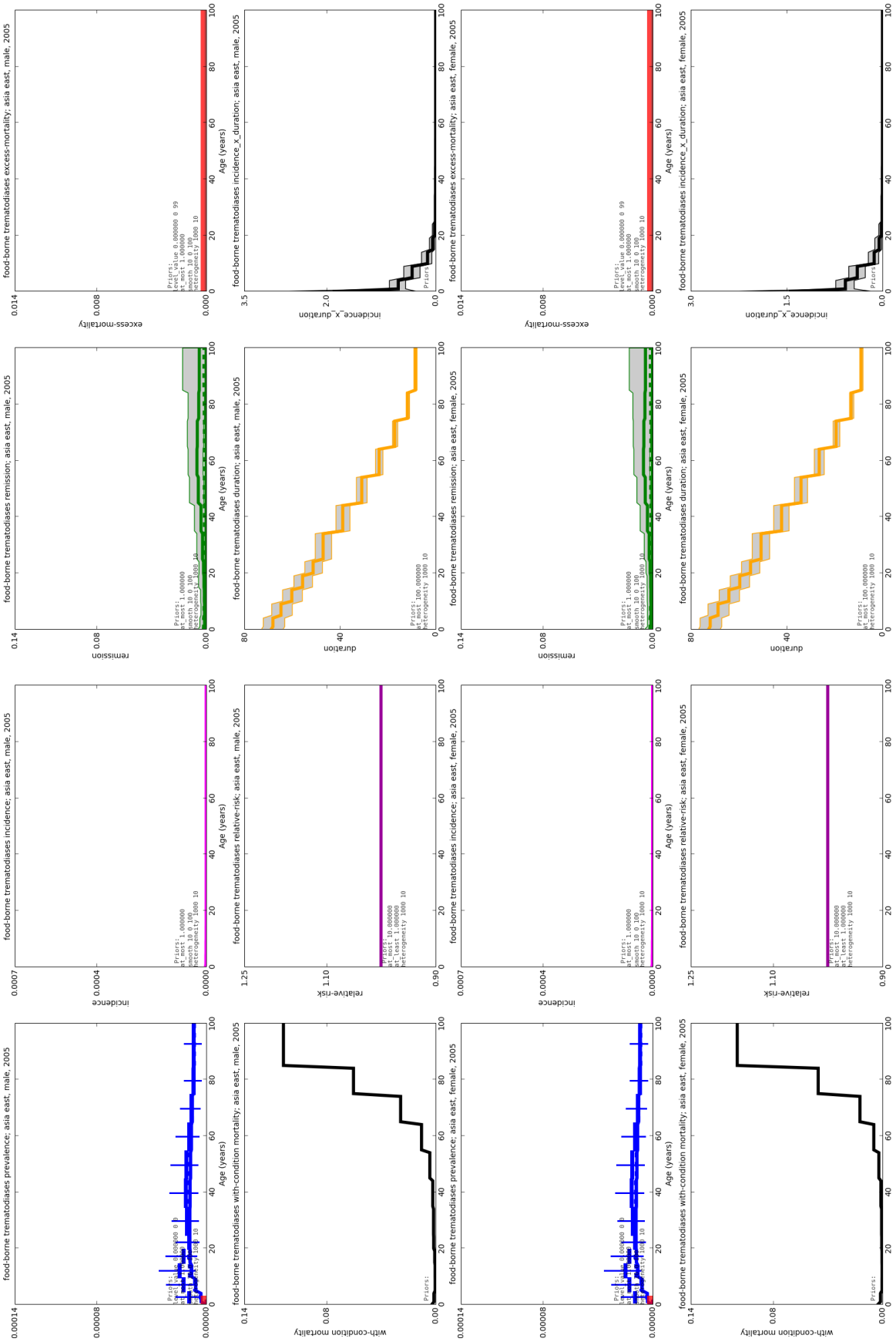
13.2.8. Webappendix 8. Continued

Heavy fasioliasis: North Africa or Middle East



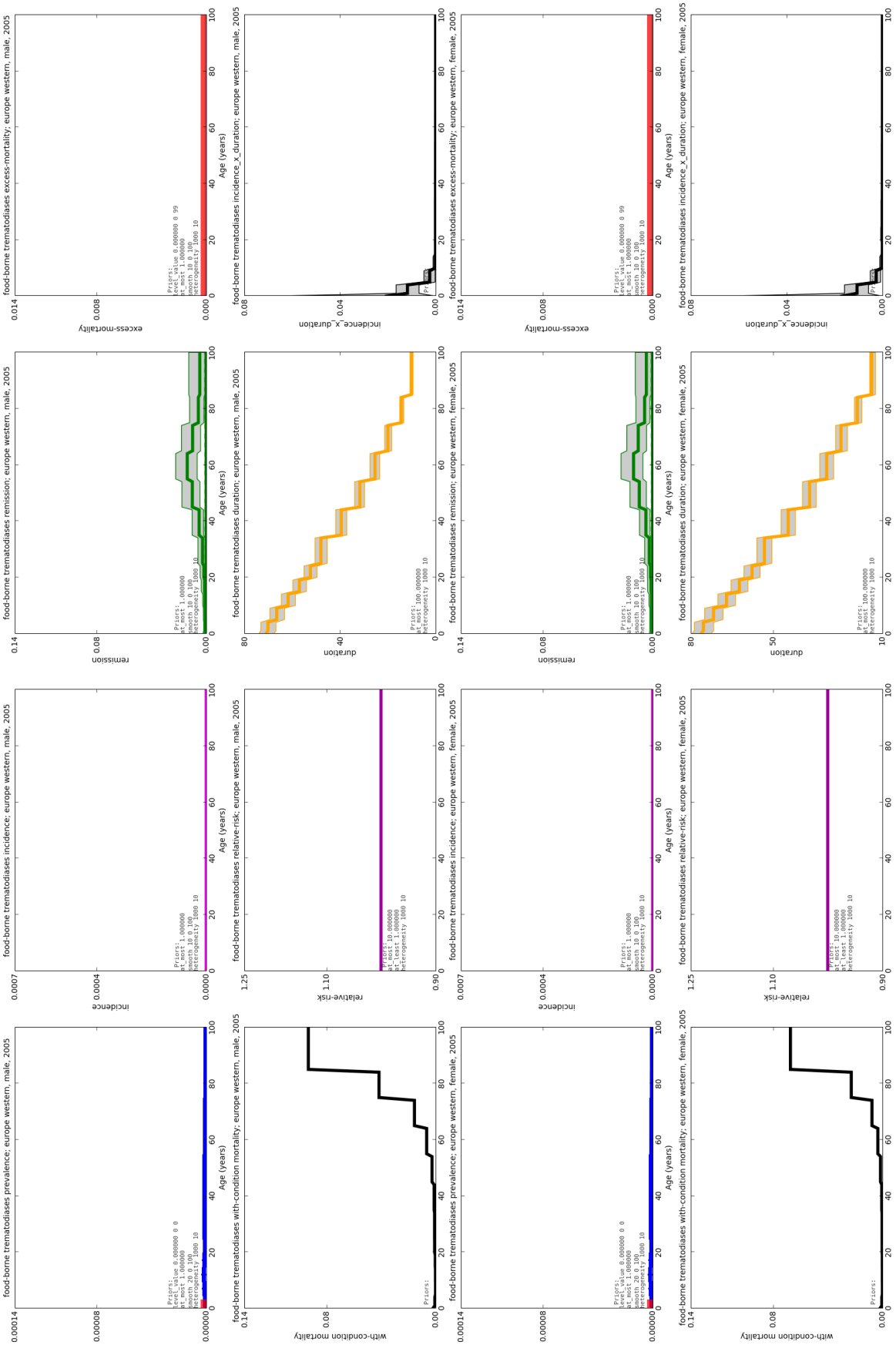
13.2.8. Webappendix 8. Continued

Heavy fasioliasis: Asia, east



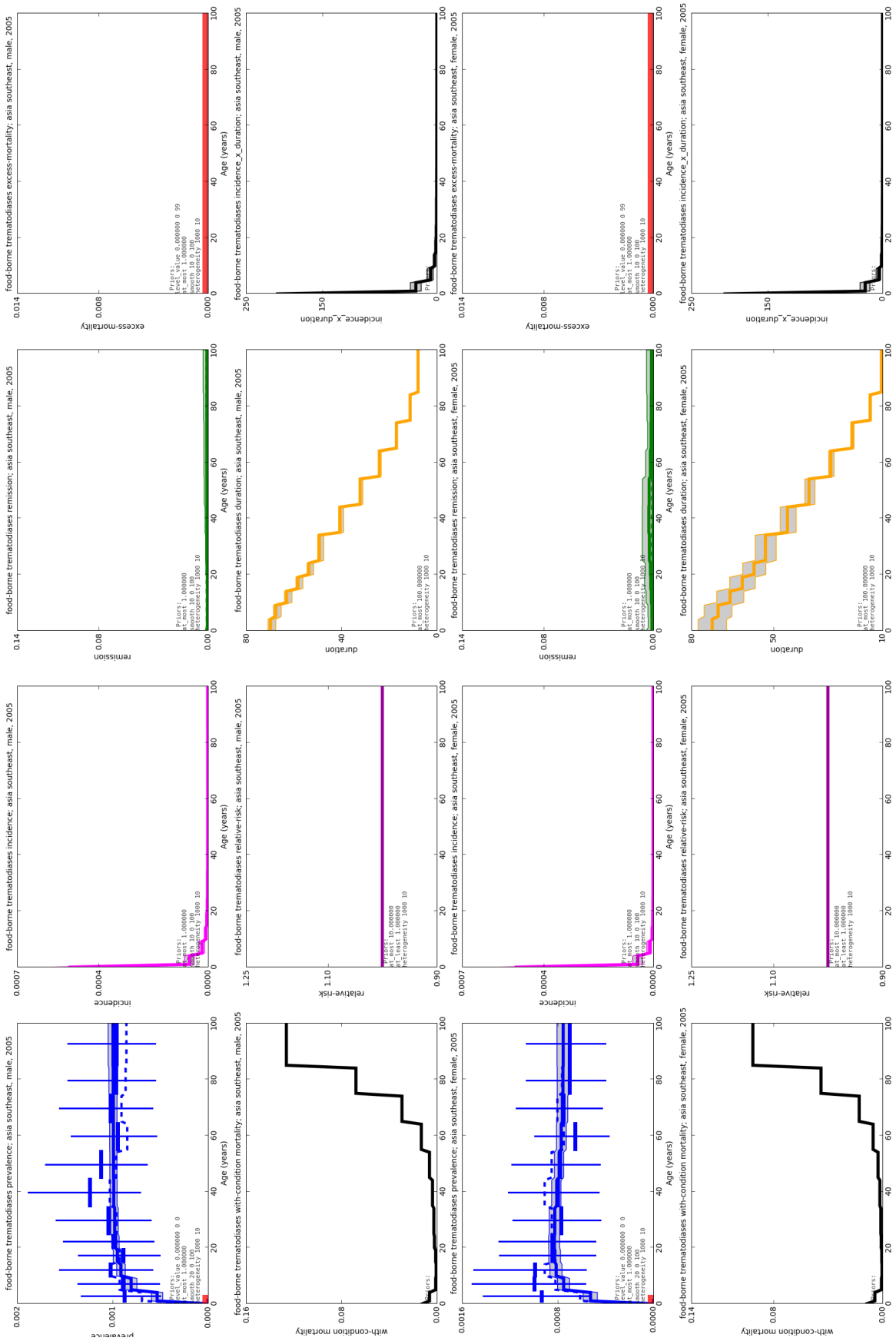
13.2.8. Webappendix 8. Continued

Heavy fasioliasis: Europe, western



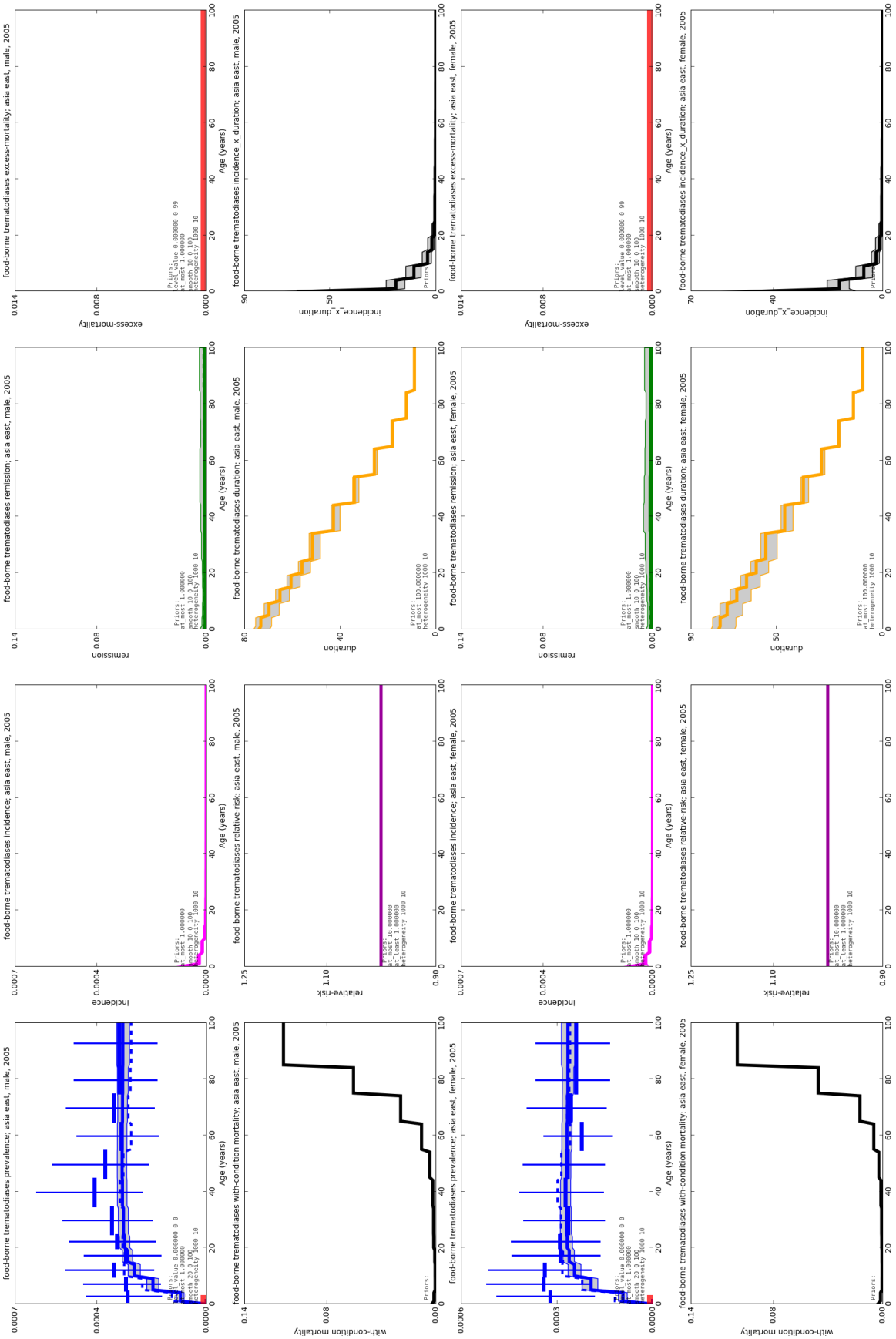
13.2.8. Webappendix 8. Continued

Heavy intestinal fluke infections: Asia, southeast



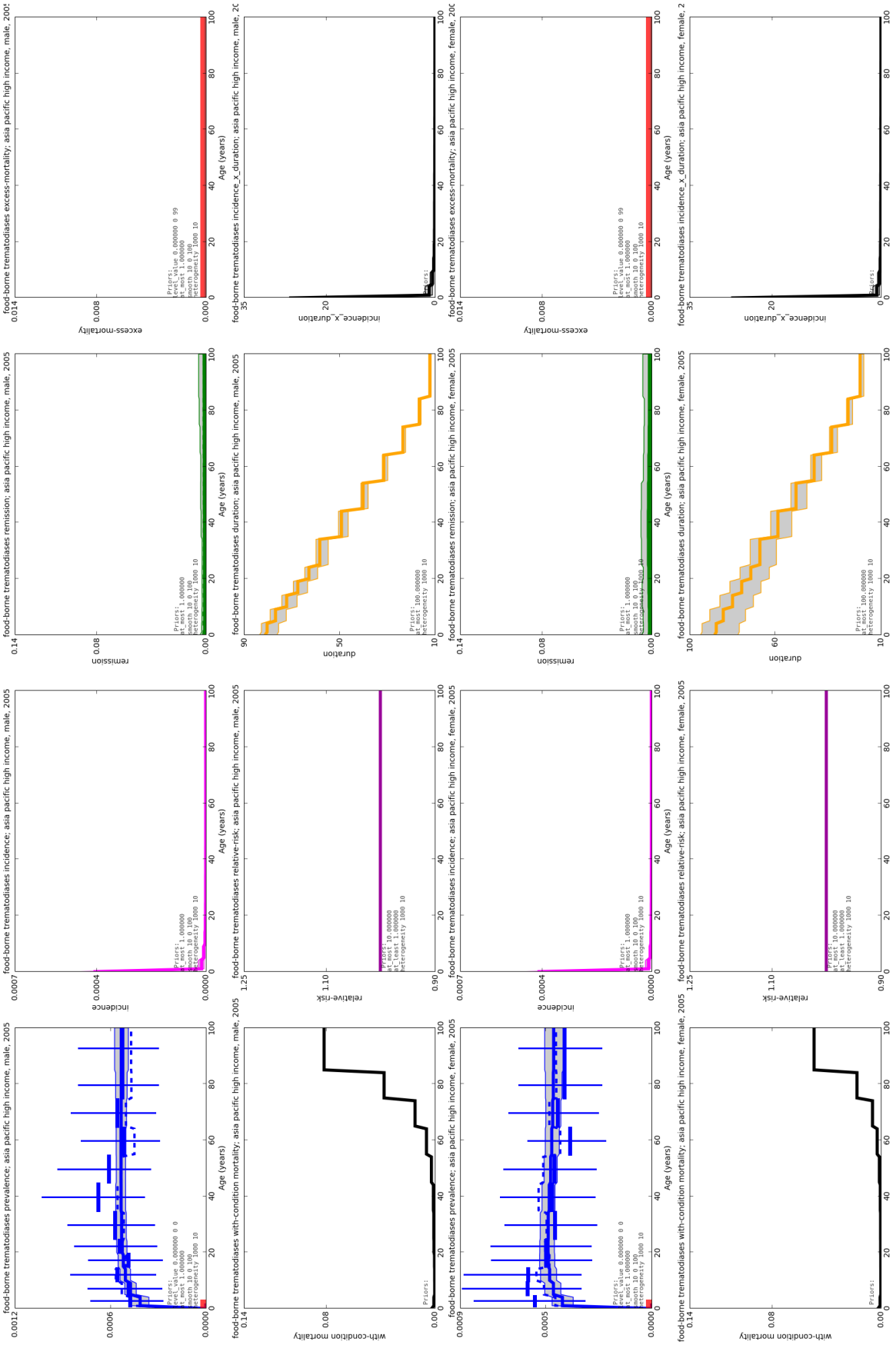
13.2.8. Webappendix 8. Continued

Heavy intestinal fluke infections: Asia, east



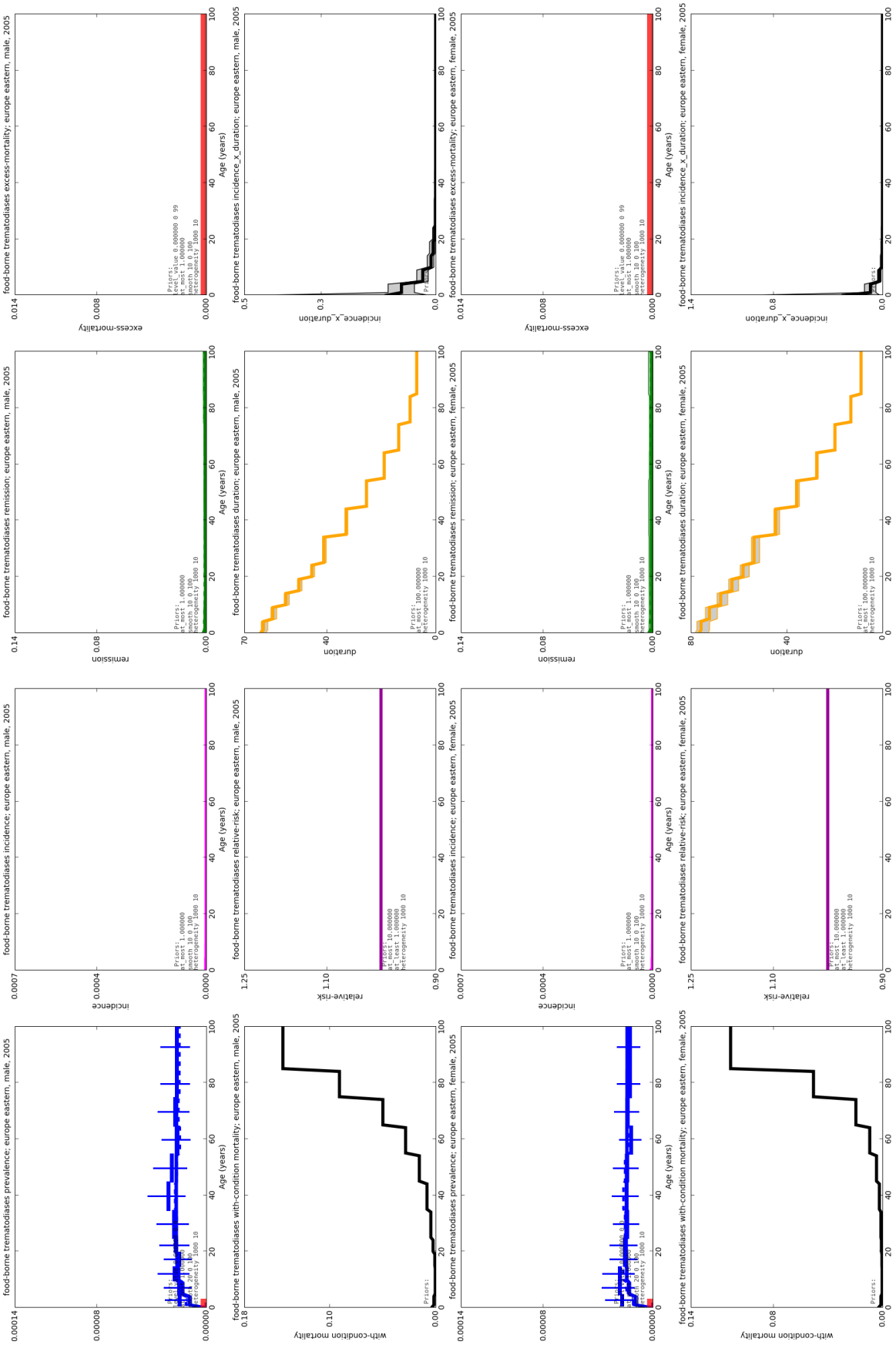
13.2.8. Webappendix 8. Continued

Heavy intestinal fluke infections: Asia Pacific, high income



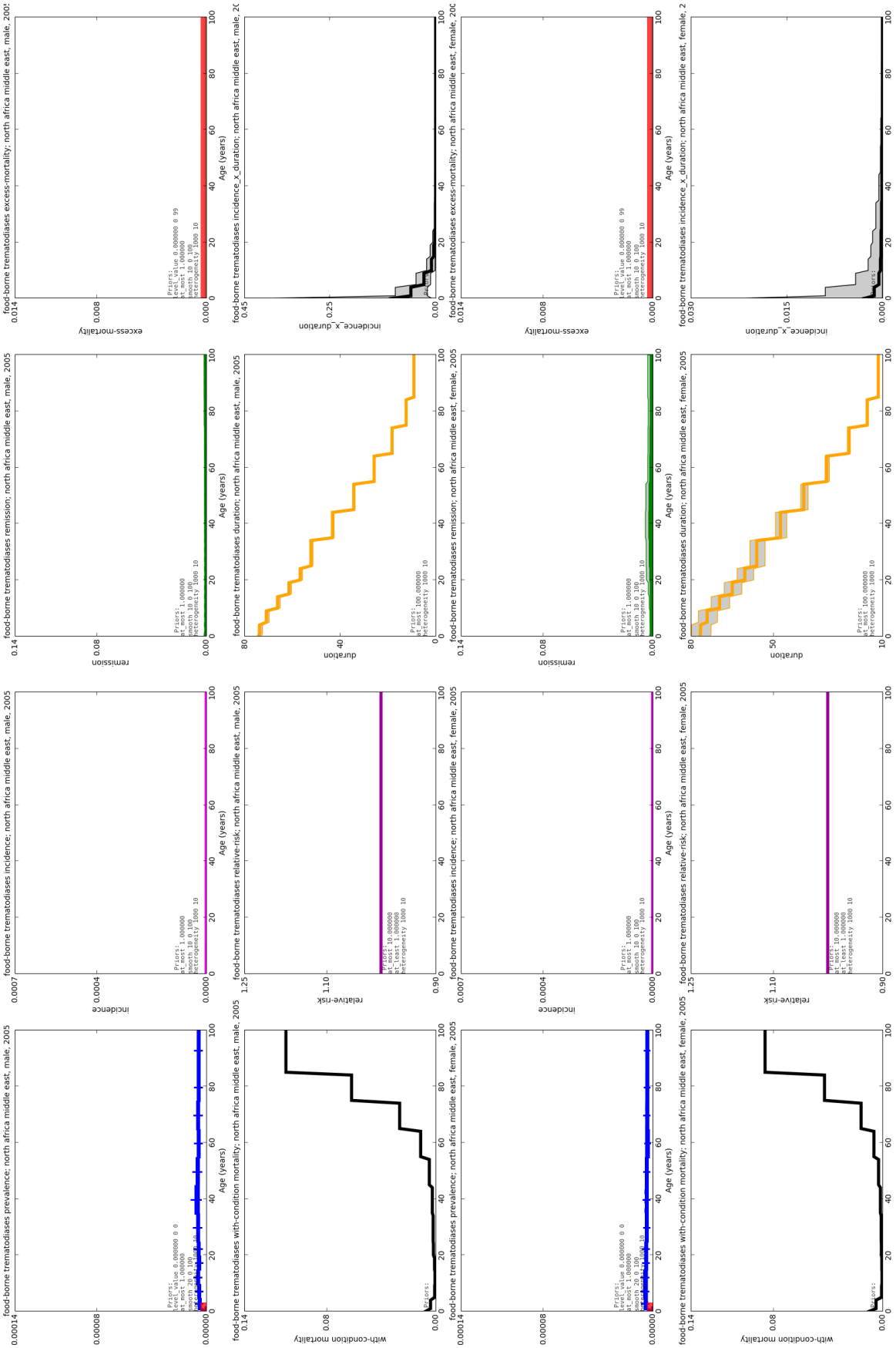
13.2.8. Webappendix 8. Continued

Heavy intestinal fluke infections: Europe, eastern



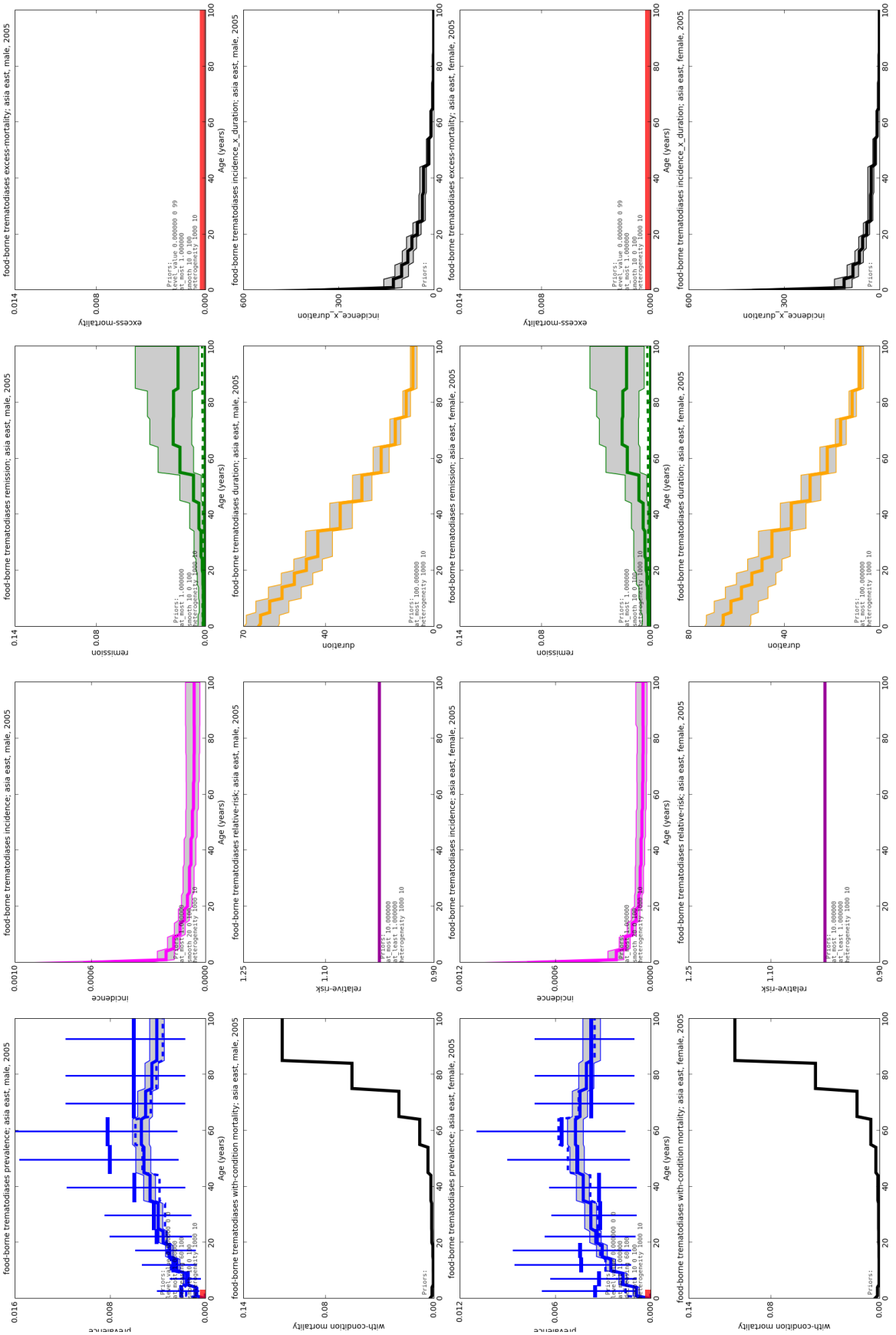
13.2.8. Webappendix 8. Continued

Heavy intestinal fluke infections: North Africa or Middle East



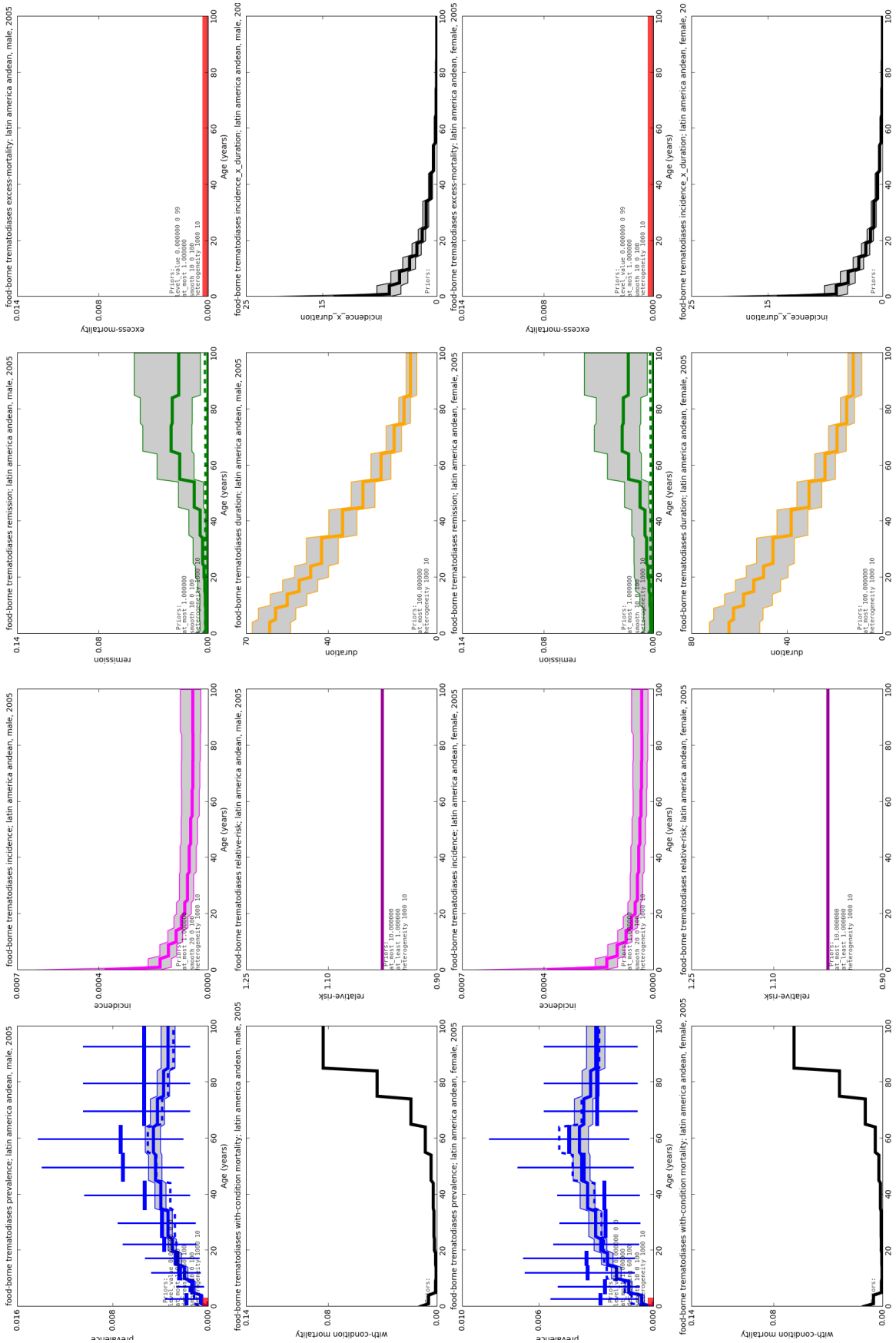
13.2.8. Webappendix 8. Continued

Heavy paragonimiasis: Asia, east



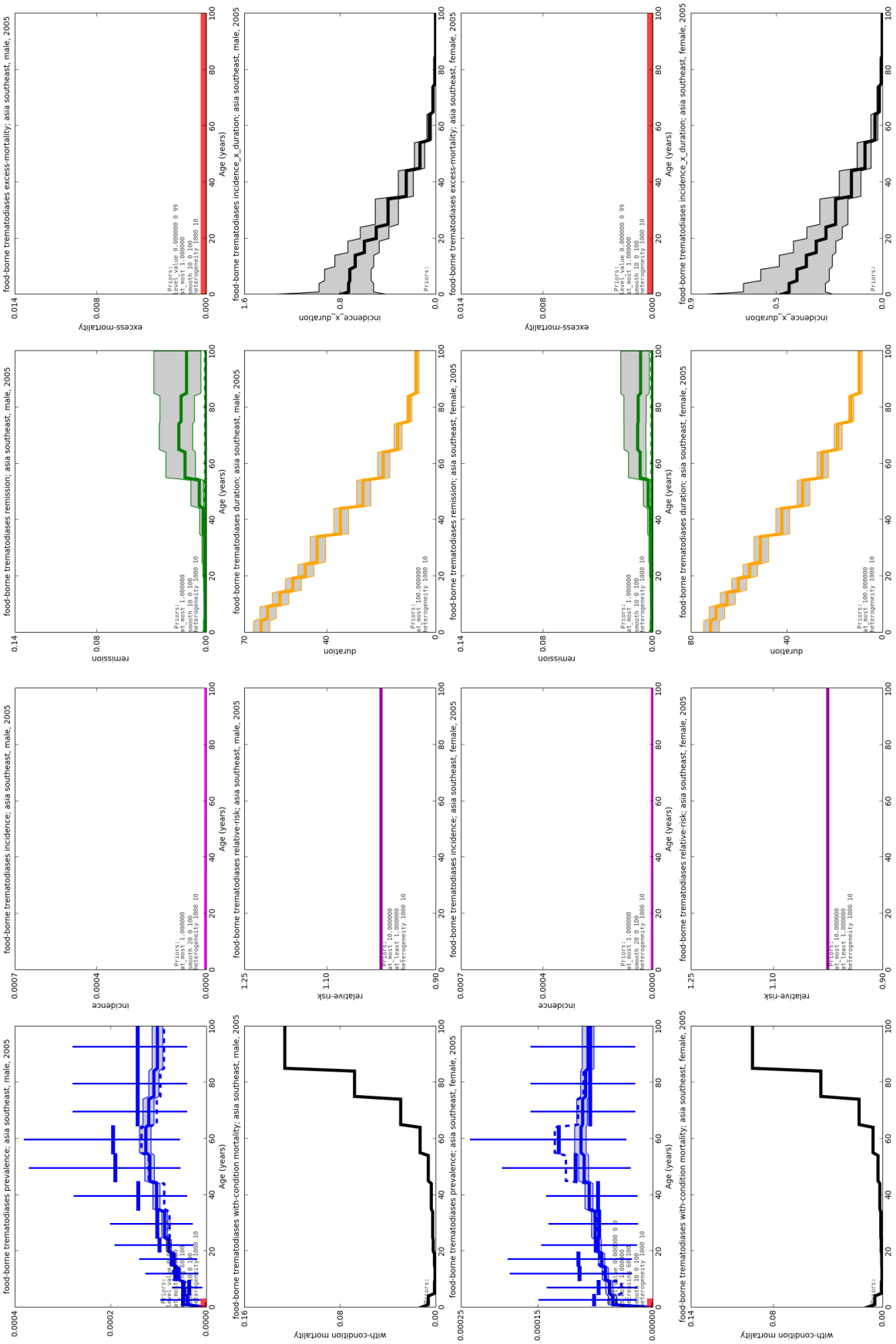
13.2.8. Webappendix 8. Continued

Heavy paragonimiasis: Latin America, Andean



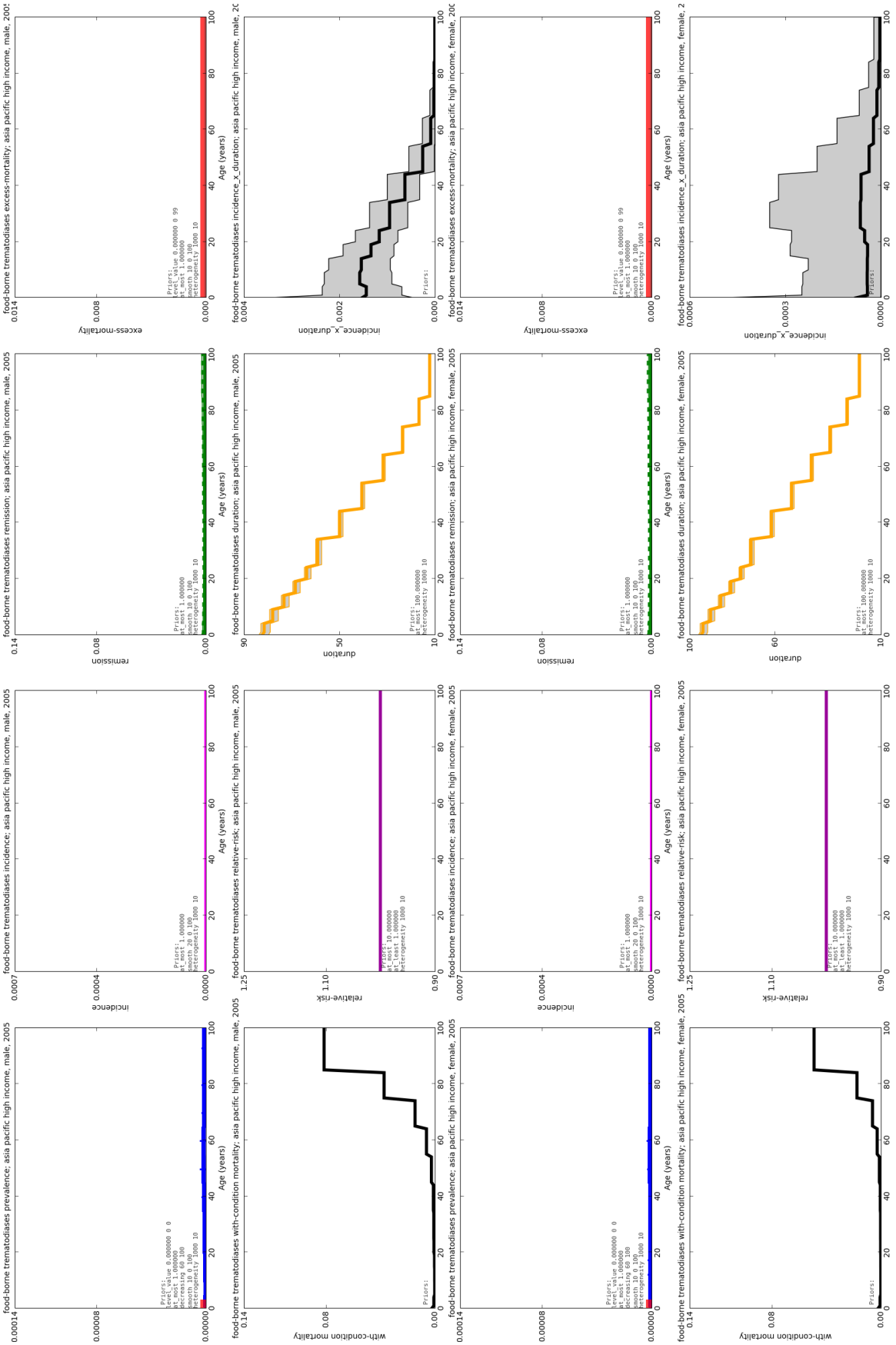
13.2.8. Webappendix 8. Continued

Heavy paragonimiasis: Asia, southeast



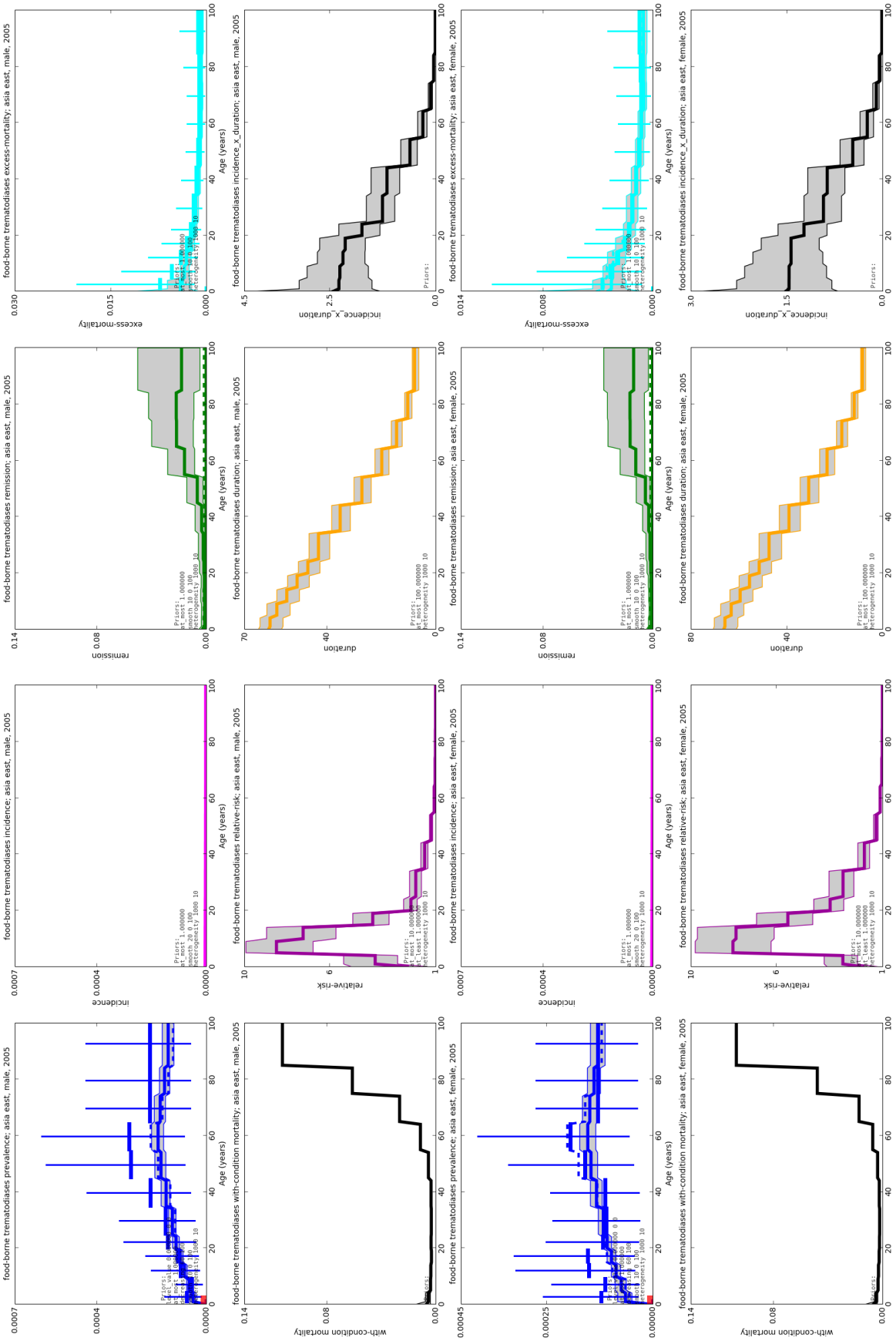
13.2.8. Webappendix 8. Continued

Heavy paragonimiasis: Asia Pacific, high income



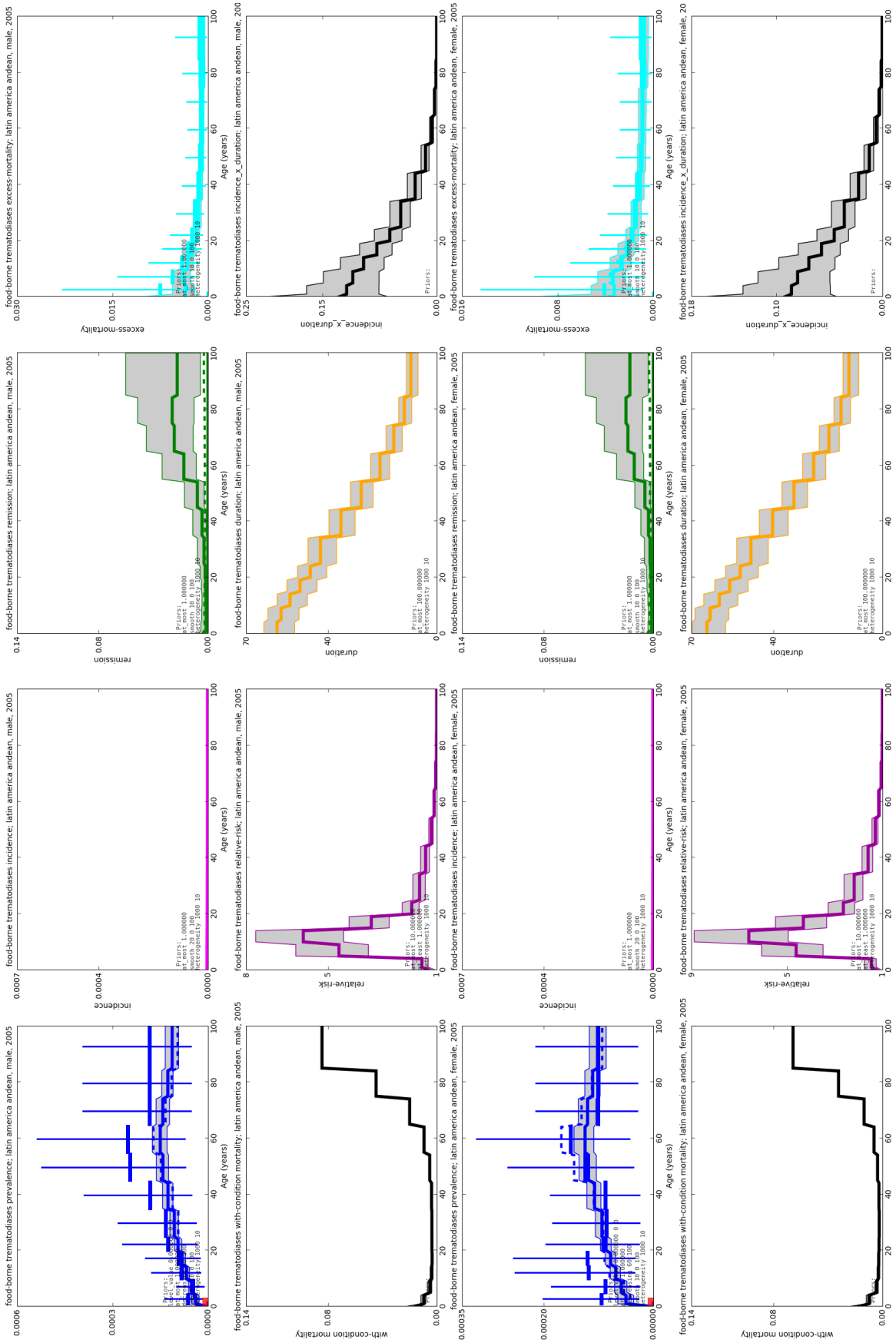
13.2.8. Webappendix 8. Continued

Cerebral paragonimiasis: Asia, east



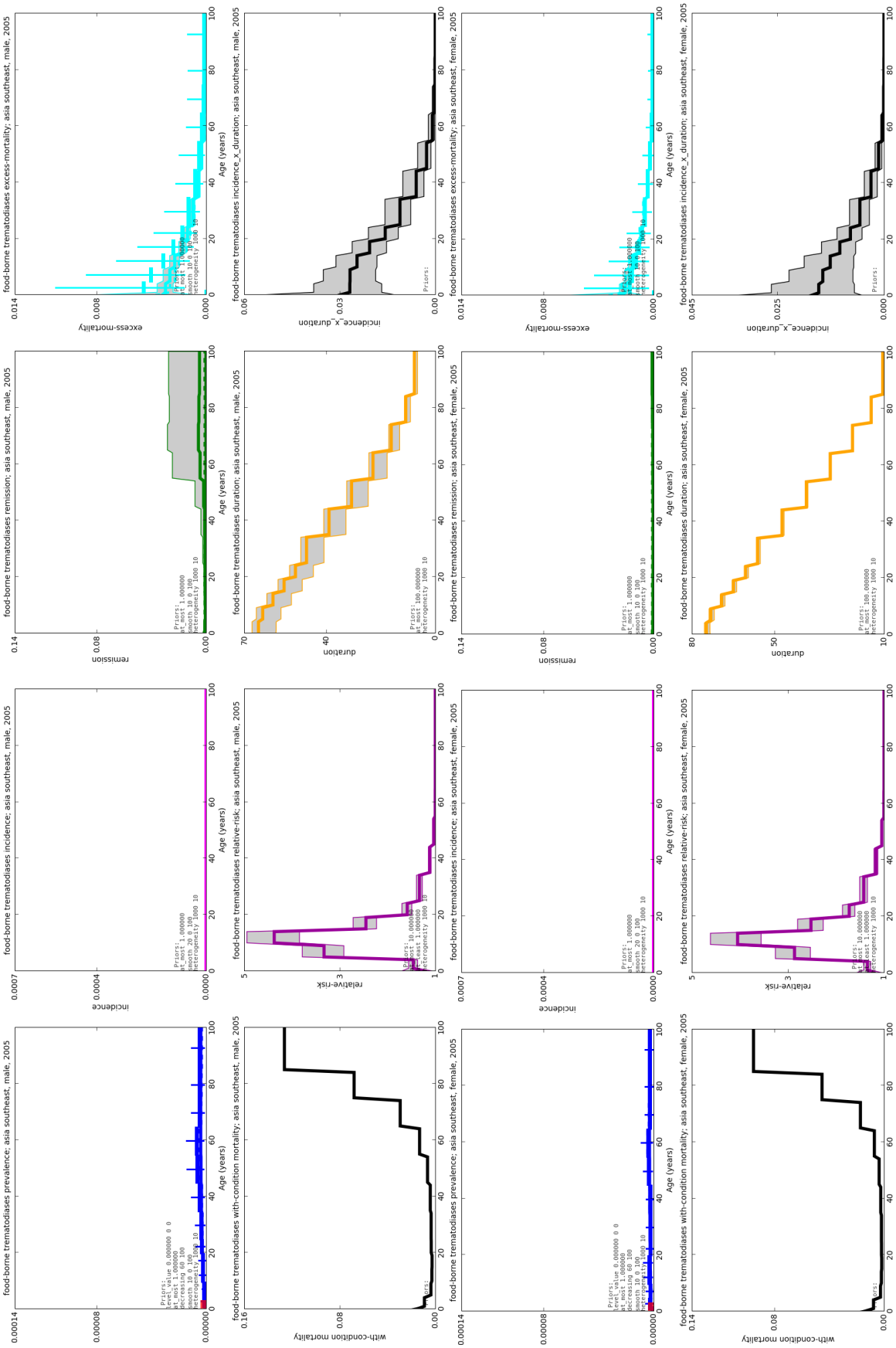
13.2.8. Webappendix 8. Continued

Cerebral paragonimiasis: Latin America, Andean



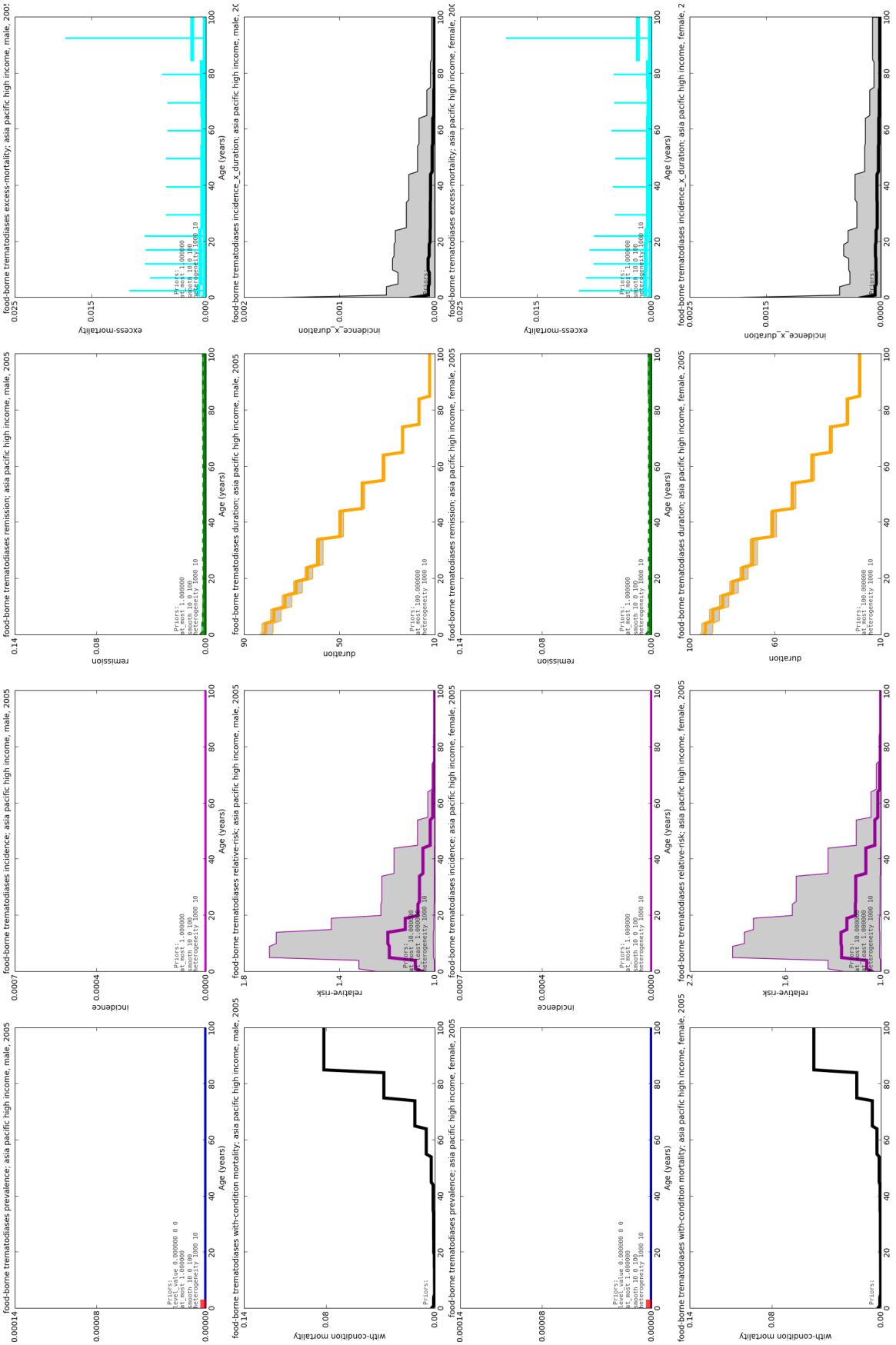
13.2.8. Webappendix 8. Continued

Cerebral paragonimiasis: Asia, southeast



13.2.8. Webappendix 8. Continued

Cerebral paragonimiasis: Asia Pacific, high income



13.2.9. Webappendix 9. Summary of parasite-specific and region-specific modelled lower and upper estimates for human food-borne trematodiasis in 2005, based on GBD 2010 study regions

Lower estimates.

Disease	GBD 2010 study region (countries and special administrative regions with cases included in the estimates)	Total number of infected[a]	Number of heavy infections	Number of cerebral infections	Number of deaths	YLD	YLL	DALYs
Clonorchiasis	Asia, east (China, Hong Kong, Macao)	12,905,956	872,036	NA	3,745	16,701	160,060	176,761
	Asia, southeast (Vietnam)	1,247,370	92,463	NA	414	2,261	19,020	21,281
	Asia Pacific, high income (South Korea)	1,157,013	78,222	NA	333	1,076	12,349	13,425
	Europe, eastern (Russia)	2,879	231	NA	1	3	40	43
	Global	15,313,219	1,042,952	NA	4,493	20,041	191,469	211,510
Opisthorchiasis	Asia, southeast (Laos, Thailand)[b]	8,028,503	283,979	NA	1,144	7,707	54,813	62,520
	Europe, eastern (Russia., Ukraine)[c]	325,160	11,236	NA	0	176	0	176
	Asia, central (Kazakhstan)[c]	44,567	1,419	NA	0	42	0	42
	Global	8,398,230	296,634	NA	1,144	7,925	54,813	62,738
Fascioliasis	Latin America, Andean (Bolivia, Ecuador, Peru)	1,378,341	132,113	NA	0	11,619	0	11,619
	North Africa or Middle East (Egypt, Iran)	1,119,812	124,747	NA	0	10,518	0	10,518
	Asia, east (China)	144,427	13,142	NA	0	226	0	226
	Europe, western (Portugal, Spain)	3,933	439	NA	0	1	0	1
	Global	2,646,515	270,441	NA	0	22,364	0	22,364
Intestinal fluke infections	Asia, southeast (Philippines, Thailand)	3,392,726	453,050	NA	0	39,562	0	39,562
	Asia, east (China)	2,691,606	331,107	NA	0	9,265	0	9,265
	Asia Pacific, high income (South Korea, Japan)	596,586	83,031	NA	0	4,898	0	4,898
	Europe, eastern (Russia)	28,790	3,944	NA	0	20	0	20
	North Africa or Middle East (Egypt)	13,841	1,924	NA	0	5	0	5
	Global	6,723,551	873,056	NA	0	53,750	0	53,750
Paragonimiasis	Asia, east (China)	22,320,640	4,393514	142,144	152	115,689	8,037	123,726
	Latin America Andean (Ecuador, Peru)	630,173	115,316	3,838	5	4,545	263	4,808
	Asia, southeast (Laos)	203,334	40,765	1,358	1	532	67	599
	Asia Pacific, high income (South Korea)	957	159	20	0	1	0	1
	Global	23,155,105	4,549,754	147,360	158	120,767	8,367	129,134
All FBT	Global	56,236,623	7,032,837	147,360	5,795	224,847	254,649	479,496

Total number of infected, number of symptomatic cases, deaths, years lived with disability (YLD), years of life lost (YLL), and disability-adjusted life years (DALYs) attributable to human food-borne trematodiasis are displayed for the different world regions in 2005. World regions are defined according to the GBD 2010 study guidelines (see reference [1] from the main text). DALYs are calculated without age-weighting or discounting (i.e., they represent so-called DALYs [0,0]). Lower and upper estimates are based on 95% CIs and credible intervals. NA = not applicable. [a]The same as the point estimates due to reasons discussed at the end of the statistical analysis section in the main text. [b]Only *O. viverrini*. [c]Only *O. felineus*.

Upper estimates.

Disease	GBD 2010 study region (countries and special administrative regions with cases included in the estimates)	Total number of infected[a]	Number of heavy infections	Number of cerebral infections	Number of deaths	YLD	YLL	DALYs
Clonorchiasis	Asia, east (China, Hong Kong, Macao)	12,905,956	1,035,093	NA	5,859	42,589	250,801	293,390
	Asia, southeast (Vietnam)	1,247,370	104,394	NA	565	5,869	26,037	31,906
	Asia Pacific, high income (South Korea)	1,157,013	92,109	NA	515	2,880	19,008	21,888
	Europe, eastern (Russia)	2,879	258	NA	1	8	58	66
	Global	15,313,219	1,231,854	NA	6,949	51,346	295,904	347,250
Opisthorchiasis	Asia, southeast (Laos, Thailand)[b]	8,028,503	349,875	NA	1,637	14,402	77,694	92,096
	Europe, eastern (Russia, Ukraine)[c]	325,160	14,313	NA	0	326	0	326
	Asia, central (Kazakhstan)[c]	44,567	1,765	NA	0	78	0	78
	Global	8,398,230	365,953	NA	1,637	14,806	77,694	92,500
Fascioliasis	Latin America, Andean (Bolivia, Ecuador, Peru)	1,378,341	172,843	NA	0	24,054	0	24,054
	North Africa or Middle East (Egypt, Iran)	1,119,812	142,118	NA	0	22,046	0	22,046
	Asia, east (China)	144,427	15,564	NA	0	951	0	951
	Europe, western (Portugal, Spain)	3,933	499	NA	0	19	0	19
	Global	2,646,515	331,024	NA	0	47,070	0	47,070
Intestinal fluke	Asia, southeast (Philippines, Thailand)	3,392,726	503,209	NA	0	67,828	0	67,828
infections	Asia, east (China)	2,691,606	378,431	NA	0	27,575	0	27,575
	Asia Pacific, high income (South Korea, Japan)	596,586	95,124	NA	0	8,008	0	8,008
	Europe, eastern (Russia)	28,790	4,364	NA	0	221	0	221
	North Africa or Middle East (Egypt)	13,841	2,102	NA	0	75	0	75
	Global	6,723,551	983,230	NA	0	103,707	0	103,707
Paragonimiasis	Asia, east (China)	22,320,640	5,482,303	180,063	352	237,885	18,574	256,459
	Latin America Andean (Ecuador, Peru)	630,173	148,773	5,080	12	10,129	724	10,853
	Asia, southeast (Laos)	203,334	47,323	1,602	2	1,096	113	1,209
	Asia Pacific, high income (South Korea)	957	195	20	0	3	0	3
	Global	23,155,105	5,678,594	186,765	366	249,113	19,411	268,524
All FBT	Global	56,236,623	8,590,655	186,765	8,952	466,042	393,009	859,051

Total number of infected, number of symptomatic cases, deaths, years lived with disability (YLD), years of life lost (YLL), and disability-adjusted life years (DALYs) attributable to human food-borne trematodiasis are displayed for the different world regions in 2005. World regions are defined according to the GBD 2010 study guidelines (see reference [1] from the main text). DALYs are calculated without age-weighting or discounting (i.e., they represent so-called DALYs [0,0]). Lower and upper estimates are based on 95% CIs and credible intervals. NA = not applicable. [a]The same as the point estimates due to reasons discussed at the end of the statistical analysis section in the main text. [b]Only *O. viverrini*. [c]Only *O. felineus*.

13.3. Effect of schistosomiasis and soil-transmitted helminth infections on physical fitness of schoolchildren in Côte d'Ivoire

13.3.1. Supporting information. Table S1. Total numbers and intensities of helminth and *Plasmodium* spp. infections among 156 schoolchildren in Côte d'Ivoire

Age	Sex	Tested	*S. haematobium*[a]				*S. mansoni*[b]				Hookworm[b]				*A. lumbricoides*[b]				*Plasmodium* spp.[c]	
Years		n	Neg.	Light	Heavy		Neg.	Light	Mod.	Heavy	Neg.	Light	Mod.	Heavy	Neg.	Light	Mod.	Heavy	Neg.	Pos.
7	M	2	2	0	0		2	0	0	0	2	0	0	0	2	0	0	0	1	1
	F	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	M	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0	0
	F	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	M	5	1	4	0		4	1	0	0	5	0	0	0	5	0	0	0	3	2
	F	6	2	2	2		2	3	1	0	6	0	0	0	6	0	0	0	1	5
10	M	12	2	7	3		4	6	1	1	11	1	0	0	12	0	0	0	6	6
	F	14	3	5	6		6	3	4	1	13	1	0	0	14	0	0	0	3	11
11	M	9	1	7	1		6	1	2	0	9	0	0	0	9	0	0	0	2	7
	F	7	2	2	3		3	2	2	0	7	0	0	0	7	0	0	0	4	3
12	M	24	2	10	12		11	9	4	0	16	8	0	0	24	0	0	0	5	19
	F	9	0	7	2		2	4	3	0	7	2	0	0	9	0	0	0	4	5
13	M	22	6	8	8		12	7	3	0	17	5	0	0	22	0	0	0	6	16
	F	17	0	11	6		6	7	4	0	16	1	0	0	16	0	1	0	3	14
14	M	10	0	5	5		6	4	0	0	8	2	0	0	9	1	0	0	3	7
	F	8	1	5	2		3	2	2	1	7	1	0	0	8	0	0	0	3	5
15	M	7	1	4	2		4	3	0	0	7	0	0	0	7	0	0	0	1	6
	F	4	0	0	4		1	2	1	0	4	0	0	0	4	0	0	0	0	4
7-15	M	91	15	45	31		49	31	10	1	75	16	0	0	90	1	0	0	27	64
7-15	F	65	8	32	25		23	23	17	2	60	5	0	0	64	0	1	0	18	47
7-15	Both	156	23	77	56		72	54	27	3	135	21	0	0	154	1	1	0	45	111

Prevalence and intensities of helminth and *Plasmodium* spp. infections among 156 children attending grades 4-6 in the primary school of Grand Moutcho II and III near Agboville, south Côte d'Ivoire in early 2010. Results are stratified by age and sex and thresholds of helminth infection intensities are in accordance with WHO guidelines (reference [36] from the main text). F = female. M = male. [a]Prevalence obtained by urine filtration method (2 consecutive urine samples per child). [b]Prevalence obtained by Kato-Katz method (2 consecutive stool samples per child with duplicate Kato-Katz thick smears per sample). [c]Prevalence obtained by rapid diagnostic test (RDT).

13.4. Questionnaire-based approach to assess schoolchildren's physical fitness and its potential role in exploring the putative impact of helminth and *Plasmodium* spp. infections in Côte d'Ivoire

13.4.1. Additional material. Additional file 1. Questionnaire employed to assess self-reported physical fitness in the present study

Two sections about physical functioning and physical role from the widely used SF-36v2 questionnaire (Medical Outcome Trust, Boston, MA, USA; Health Assessment Lab, Boston, MA, USA; QualityMetric, Lincoln,, RI, USA; references [14,18] from the main text) were used as templates, adapted to the specific study setting, pre-tested and further revised.

Cher élève, chère élève,

Nous avons rédigé 14 brèves questions concernant ton avis sur ta forme physique. Ce n'est pas un test avec des bonnes ou des fausses réponses. Pour nous, il est plus important d'apprendre comment tu vas et c'est seulement ton honnête opinion qui est importante. Alors, nous te prions de remplir le questionnaire suivant complètement.

1. Pour commencer, lis chaque question.
2. Assure toi que tu comprends toutes les questions. Si tu n'es pas sûr(e), tu peux toujours poser des questions à l'équipe ou à l'instituteur.
3. Contrôle toutes les réponses données, choisis la réponse qui est la plus vraie pour ta situation et puis marque le box correspondant □ avec une croix.
4. Choisis seulement une réponse par question.

Tout d'abord, nous avons besoin de ton nom.

Ecris ton nom ici: _____

Tu trouves en suivant les 14 brèves questions concernant ton avis sur ta forme physique. Chaque question décrit les activités quotidiennes au cours desquelles tu peux rencontrer des problèmes comme l'essoufflement, une fatigue ou d'épuisement à cause de ta forme physique. Maintenant c'est à toi de choisir la réponse qui est la plus vraie pour ta situation.

1) *As-tu des problèmes pour faire des activités très fatigantes, comme par exemple courir très vite, soulever des choses très lourdes ou jouer au foot sans arrêter?*
□ Oui, beaucoup de problèmes. □ Oui, quelques problèmes. □ Non, pas de problème.

2) *As-tu des problèmes de faire des activités moyennement fatigantes, comme par exemple courir lentement, bouger une table ou jouer à cache-cache?*
□ Oui, beaucoup de problèmes. □ Oui, quelques problèmes. □ Non, pas de problème.

3) *As-tu des problèmes pour soulever ou porter ton sac à dos ou sac de riz de 5 kilogramme?*
□ Oui, beaucoup de problèmes. □ Oui, quelques problèmes. □ Non, pas de problème.

4) *As-tu des problèmes pour monter brièvement sur une colline basse?*
□ Oui, beaucoup de problèmes. □ Oui, quelques problèmes. □ Non, pas de problème.

5) *As-tu des problèmes pour monter sur une colline raide pendant un temps prolongé?*
□ Oui, beaucoup de problèmes. □ Oui, quelques problèmes. □ Non, pas de problème.

6) *As-tu des problèmes pour te pencher en avant, te baisser ou t'agenouiller?*
□ Oui, beaucoup de problèmes. □ Oui, quelques problèmes. □ Non, pas de problème.

7) *As-tu des problèmes pour aller à pied de l'école de Moutcho jusqu'au marché de Moutcho (environs 100 mètres)?*
□ Oui, beaucoup de problèmes. □ Oui, quelques problèmes. □ Non, pas de problème.

8) *As-tu des problèmes pour aller à pied de l'école de Moutcho jusqu'au bout de village Moutcho (environs 400 - 600 mètres)?*
□ Oui, beaucoup de problèmes. □ Oui, quelques problèmes. □ Non, pas de problème.

9) *As-tu des problèmes pour aller à pied de l'école de Moutcho jusqu' à l'école Nakoi (environs 1'000 mètres)?*
□ Oui, beaucoup de problèmes. □ Oui, quelques problèmes. □ Non, pas de problème.

10) *As-tu des problèmes pour te baigner, te laver ou t'habiller?*
□ Oui, beaucoup de problèmes. □ Oui, quelques problèmes. □ Non, pas de problème.

11) *As-tu eu des problèmes pour apprendre tes leçons, aider quelqu'un de ta famille ou jouer avec tes amis aussi long temps que d'habitude à cause de ta forme physique pendant le dernier mois?*
□ Oui, toujours. □ Oui, souvent. □ Oui, mais rarement. □ Non, jamais.

12) *As-tu eu des problèmes à faire la même quantité de devoirs à l'école ou à la maison comme d'habitude à cause de ta forme physique pendant le dernier mois?*
□ Oui, toujours. □ Oui, souvent. □ Oui, mais rarement. □ Non, jamais.

13) *Pouvais-tu seulement faire certaines activités quotidiennes (comme apprendre pour l'école, aider quelqu'un de ta famille ou jouer) mais pas toutes à cause de ta forme physique pendant le dernier mois?*
□ Oui, toujours. □ Oui, souvent. □ Oui, mais rarement. □ Non, jamais.

14) *As-tu eu besoin de faire plus d'effort que d'habitude pour apprendre tes leçons, aider quelqu'un de ta famille ou jouer avec tes amis à cause de ta forme physique pendant le dernier mois?*
□ Oui, toujours. □ Oui, souvent. □ Oui, mais rarement. □ Non, jamais.

Et voilà, c'est déjà fini. Merci beaucoup pour ta merveilleuse collaboration.

13.5. Schistosomiasis, soil-transmitted helminthiasis, and socio-demographic factors influence quality of life of adults in Côte d'Ivoire

13.5.1. Supporting information. Alternative language abstract S1 in French. Schistosomiase, géohelminthiases et facteurs socio-démographiques influencent la qualité de vie des adultes en Côte d'Ivoire

Contexte: Les estimations du fardeau attribué aux différentes maladies sont aujourd'hui largement utilisées en santé publique pour établir les priorités. Parmi ces indicateurs, le nombre d'années de vie corrigées du facteur d'invalidité (AVCI) est le plus couramment employé. Cependant, cet indicateur fait l'objet d'une critique continue du fait que pour le calculer, l'estimation de l'invalidité subie par un patient est essentielle et cette dernière représente un sujet encore largement débattu.

Méthodologie: Une enquête épidémiologique transversale a été conduite dans le site de surveillance démographique et de santé (SSDS) établi en 2008 à Taabo, au centre sud de la Côte d'Ivoire. Cette enquête avait pour objet à partir de données collectées au niveau de la population, de rechercher de nouvelles preuves sur le handicap causé par la schistosomiase et les géohelminthiases. Les résultats des examens parasitologiques de selles, d'urine et de sang ont été associés aux résultats d'un questionnaire sur la qualité de vie de 187 adultes. Un modèle de régression linéaire multiple a été utilisé pour identifier les associations significatives, en considérant aussi des caractéristiques socio-démographiques obtenues à partir de la base de données du SSDS de Taabo.

Principaux Résultats: Les prévalences des ankylostomes, *Plasmodium* spp., *Trichuris trichiura*, *Schistosoma haematobium* et *Schistosoma mansoni* ont été de 39,0 %, 18,2 %, 2,7 %, 2,1 % et 2,1 %, respectivement. Les infestations par *S. mansoni* et *T. trichiura* de toute intensité, réduisent l'auto-évaluation de la qualité de vie des participants de 16 points (intervalle de confidence (IC) à 95 %: 4-29 points) et 13 points (IC 95 %: 1-24 points) respectivement sur une échelle de 0 (la plus mauvaise qualité de vie) à 100 points (la mieux qualité de vie). Le seul autre effet statistiquement significatif était une augmentation de 1 point (IC 95 %: 0.1-2 points) sur l'échelle, qui mesure la qualité de vie, si un indice de richesse calculé par nous-même augmentait d'une unité.

Conclusion: En considérant aussi des caractéristiques socio-démographiques, nous avons montré sur la base d'associations statistiquement et significatives, l'impact négatif de la schistosomiase et des géohelminthiases sur l'auto-évaluation de la qualité de vie chez les

adultes. Ces résultats démontrent la pertinence d'un questionnaire générique sur la qualité de la vie dans un tel contexte et incitent à une enquête plus approfondie sur le handicap induit par helminthiases.

Traduction: Kigbafori D. Silué et Eliézer K. N'Goran.

13.5.2. Supporting information. Text S2. Questionnaire for evaluating the health state of individuals (in French)

Enquête pour évaluer l'état de santé

Questionnaire pour les participents à l'enquête transversal au SSD de Taabo en Juin 2010.

Cher(e) participant(e),

Nous avons rédigé quelques questions concernant votre avis sur votre état de santé et vos activités quotidiennes. Ces questions ne sont pas un test avec des bonnes et des mauvaises réponses. Pour nous, il est plus important de savoir comment vous allez et seule votre opinion personnelle et honnête nous intéresse. Nous vous prions donc de nous aider à remplir le questionnaire complètement.

Village/Campement :								
Date :	**Nom de l'enquêteur :**							
Numéro d'identification du participant								

Facteur de risque (6)
Indiquez le numéro correct (1, 2 ou 9) pour chaque réponse prévue à la gauche.

1) Quelles activités liées à l'eau (de rivières, lacs, marigot etc.) avez-vous pratiqué durant ces 4 dernières semaines ? (1=oui / 2=non / 9=ne sait pas)	faire la lessive	___
	faire la vaisselle	___
	se laver	___
	nager	___
	cuisiner	___
	laver les enfants	___
	traverser les rivières	___
	pêcher au filet	___
	pêcher à l'hameçon	___
	cultiver du riz	___
	pratiques religieuses	___
	autres :……..	___
2) Quelle eau buvez-vous ? (1=oui / 2=non / 9=ne sait pas)	eau de marigot, ruisseau, rivière	___
	eau de pluie	___
	eau courrant / robinet	___
	eau en bouteille / eau minérale / awa	___
	autres :……..	___
3) Ces 4 dernières semaines, avez-vous utilisé… (1=oui / 2=non / 9=ne sait pas)	une moustiquaire	___
	des insecticides (p. ex. timor)	___
	moustico	___
	autres :……..	___

4) Est-ce que vous utilisez du savon pour… (1=oui / 2=non / 9=ne sait pas)	faire la lessive	
	faire la vaisselle	
	vous laver	
	vous laver les mains avant de manger	
	vous laver les mains après les selles	
	laver les mains au retour du travail	
5) De temps en temps, mangez-vous… (1=oui / 2=non / 9=ne sait pas)	de la viande crue	
	des poisons crus	
	des fruits crus	
	des légumes crus	
6) Quels animaux possédez-vous ? (1=oui / 2=non / 9=ne sait pas)	chien	
	poule / volaille	
	lapin	
	cobaye	
	cochon	
	cabri	
	mouton	
	vache / buffle	
	autres :……	

Signes & Symptômes (2)

7) Avez-vous expérimenté un ou plusieurs signes ou symptômes suivants durant ces 4 dernières semaines? (1=oui / 2=non / 9=ne sait pas)	sang dans les selles	
	sang dans l'urine	
	mal de ventre	
	ballonnement du ventre	
	perte de l'appétit	
	mal de tête	
	troubles visuels	
	problème pour articuler/ parler	
	fièvre/ corps qui chauffe	
	faiblesse/ fatigue	
	vomissement	
	vertige	
	diarrhée	
	douleur en pissant	
	perte de poids	
	boutons ou tache sur la peau	
	mal à la poitrine	
	problème pour respirer	
	toux	
	corps qui gratte	
	partie du corps enflée	
	mal de rein	
	autres :……	

8) Quelles sont les maladies fréquentes dans votre ménage ? (1=oui / 2=non / 9= ne sait pas)	Bilharziose ou schistosomiase	
	Tuberculose	
	Diarrhée	
	Onchocercose	
	VIH / SIDA	
	Méningite	
	Filariose / éléphantiasis	
	Paludisme	
	Ulcère de buruli	
	Vers intestinaux	
	Lèpre	
	Je ne connais pas ces maladies	

Qualité de vie (adultes : WHOQOL bref (24))
Marquez la réponse qui est la plus vraie pour chaque question.

9) Vous sentez-vous en bonne santé ?	Non, pas du tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
10) Avez vous eu assez d'énergie durant ces 4 dernières semaines pour mener votre vie quotidienne ?	Non, pas du tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
11) Avez-vous eu assez d'argent pour acheter tout ce dont vous aviez besoin durant ces 4 dernières semaines ?	Non, pas du tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
12) Avez-vous eu assez de temps libre durant ces 4 dernières semaines ?	Non, pas du tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
13) Êtes-vous satisfait de votre capacité de travail ?	Non, pas du tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
14) Êtes-vous satisfait de vos relations personnelles (par exemple avec vos amis ou votre famille) ?	Non, pas de tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
15) Êtes-vous satisfait du support de vos amis ?	Non, pas de tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
16) Êtes-vous satisfait de votre logement ?	Non, pas de tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
17) Êtes-vous satisfait de votre accès au centre de santé le plus proche ?	Non, pas de tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
18) Êtes-vous satisfait de vos possibilités de transport ?	Non, pas de tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐

19) Êtes-vous content avec vous et votre situation en générale ?	Non, pas de tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐

20) Combien de fois avez-vous pris des médicaments durant ces 4 dernières semaines ?	Jamais ☐	Rarement ☐	Souvent ☐	Toujours ☐
21) Combien de fois vous êtes-vous réjouit de votre vie durant ces 4 dernières semaines?	Jamais ☐	Rarement ☐	Souvent ☐	Toujours ☐
22) Combien de fois avez-vous pensé que votre vie avait un sens durant ces 4 dernières semaines?	Jamais ☐	Rarement ☐	Souvent ☐	Toujours ☐
23) Combien de fois avez-vous eu des problèmes pour vous concentrer durant ces 4 dernières semaines ?	Jamais ☐	Rarement ☐	Souvent ☐	Toujours ☐
24) Combien de fois ne vous êtes vous pas sentis en sécurité durant ces 4 dernières semaines?	Jamais ☐	Rarement ☐	Souvent ☐	Toujours ☐
25) Combien de fois avez-vous eu des sentiments négatifs, comme par exemple la peur, le désespoir, la tristesse ou la dépression ?	Jamais ☐	Rarement ☐	Souvent ☐	Toujours ☐

26) Avez vous souffert de douleurs, durant ces 4 dernières semaines, qui vous ont handicapées dans vos activités quotidiennes ?	Non, jamais ☐	Oui, mais rarement ☐	Oui, souvent ☐	Oui, toujours ☐
27) Avez-vous eu de la peine à marcher durant ces 4 dernières semaines?	Non, jamais ☐	Oui, mais rarement ☐	Oui, souvent ☐	Oui, toujours ☐
28) Avez-vous bien dormi durant ces 4 dernières semaines?	Non, jamais ☐	Oui, mais rarement ☐	Oui, souvent ☐	Oui, toujours ☐
29) Avez-vous eu des problèmes pour exécuter vos activités quotidiennes durant ces 4 dernières semaines?	Non, jamais ☐	Oui, mais rarement ☐	Oui, souvent ☐	Oui, toujours ☐

30) Comment jugez-vous votre qualité de vie, en général ?	Très bien ☐	Bien ☐	Mal ☐	Très mal ☐

Merci beaucoup de votre merveilleuse collaboration!!!

13.5.3. Supporting information. Text S3. Questionnaire for evaluating the health state of individuals (unofficial translation into English)

Survey to evaluate the health status

Questionnaire for participants of the cross-sectional survey in the Taabo HDSS in June 2010

Dear participant,

We prepared some questions regarding your opinion about your personal health status and daily activities. These questions are not a test with right or wrong answers. For us, it is most important to know how you feel and we are only interested in your personal and honest opinion. We would therefore like to ask you to help us complete the following questionnaire.

Name of village/hamlet:								
Date:	**Name of field enumerator:**							
ID number of participant								

Risk Factors (6)
Note the correct number (1, 2, or 9) for each response indicated on the left.

1) Which water-related (rivers, lakes, ponds, etc.) activities did you do during the last 4 weeks? (1=yes / 2=no / 9=don't know)	do the laundry	___
	wash the dishes	___
	wash yourself	___
	swimming	___
	cooking	___
	wash the children	___
	cross the rivers	___
	fishing with net	___
	fishing with fishing-rod	___
	cultivate rice	___
	religious worship	___
	others:……..	___
2) Which water do you drink? (1=yes / 2=no / 9=don't know)	water from rivers, lakes, ponds	___
	rain water	___
	tap water	___
	bottled water / mineral water / awa	___
	others:……..	___
3) During the last 4 weeks, did you use… (1=yes / 2=no / 9=don't know)	a mosquito net	___
	insecticides (e.g., Timor)	___
	moustico	___
	others:……..	___

4) Do you use soap for… (1=yes / 2=no / 9=don't know)	doing the laundry	___
	washing the dishes	___
	washing yourself	___
	washing your hands before eating	___
	washing your hands after defecation	___
	washing your hands when returning from work	___
5) From time to time, do you eat… (1=yes / 2=no / 9=don't know)	uncooked meat	___
	uncooked fish	___
	uncooked fruits	___
	uncooked vegetables	___
6) What animals do you own? (1=yes / 2=no / 9=don't know)	dog	___
	chicken / poultry	___
	rabbit	___
	guinea pig	___
	pig	___
	goat	___
	sheep	___
	cow / buffalo	___
	others:……	___

Signs & Symptoms (2)

7) Did you suffer from one or several of the following signs and symptoms during the last 4 weeks? (1=yes / 2=no / 9=don't know)	blood in the stool	___
	blood in the urine	___
	abdominal pain	___
	flatulence	___
	loss of appetite	___
	headache	___
	impaired vision	___
	problems to articulate / speak	___
	fever / hot body	___
	weakness / fatigue	___
	vomiting	___
	vertigo	___
	diarrhea	___
	pain when urinating	___
	weight loss	___
	spots or pimples on the skin	___
	chest pain	___
	problems to breathe	___
	cough	___
	itching body	___
	part of the body swollen	___
	kidney pain	___
	others :……	___

8) What are frequent diseases in your household? (1=yes / 2=no / 9=don't know)	Bilharzia or schistosomiasis	
	Tuberculosis	
	Diarrhea	
	Onchocerciasis	
	HIV / AIDS	
	Meningitis	
	Filariasis/elephantiasis	
	Malaria	
	Buruli ulcer	
	Intestinal helminths	
	Leprosy	
	I don't know these diseases	

Quality of life (adults: WHOQOL bref (24))
Mark the most appropriate response for each question.

9) Do you feel that you are in good health?	No, not at all ☐	More or less ☐	Yes, most of the time ☐	Yes, absolutely ☐
10) Did you have enough energy to complete your daily tasks during the last 4 weeks?	No, not at all ☐	More or less ☐	Yes, most of the time ☐	Yes, absolutely ☐
11) Did you have enough money to buy all things that you needed during the last 4 weeks?	No, not at all ☐	More or less ☐	Yes, most of the time ☐	Yes, absolutely ☐
12) Did you have enough leisure time during the last 4 weeks?	No, not at all ☐	More or less ☐	Yes, most of the time ☐	Yes, absolutely ☐
13) Are you satisfied with your working capacity?	No, not at all ☐	More or less ☐	Yes, most of the time ☐	Yes, absolutely ☐
14) Are you satisfied with your personal relationships (for instance with your friends or family)?	No, not at all ☐	More or less ☐	Yes, most of the time ☐	Yes, absolutely ☐
15) Are you satisfied with the support of your friends?	No, not at all ☐	More or less ☐	Yes, most of the time ☐	Yes, absolutely ☐
16) Are you satisfied with your housing?	No, not at all ☐	More or less ☐	Yes, most of the time ☐	Yes, absolutely ☐
17) Are you satisfied with the accessibility of the nearest health center?	No, not at all ☐	More or less ☐	Yes, most of the time ☐	Yes, absolutely ☐
18) Are you satisfied with the means of transportation that are available for you?	No, not at all ☐	More or less ☐	Yes, most of the time ☐	Yes, absolutely ☐

19) In general, are you satisfied with you and your situation?	No, not at all ☐	More or less ☐	Yes, most of the time ☐	Yes, absolutely ☐

20) How often did you take drugs during the last 4 weeks?	Never ☐	Rarely ☐	Often ☐	Always ☐
21) How often were you happy about / did you enjoy your life during the last 4 weeks?	Never ☐	Rarely ☐	Often ☐	Always ☐
22) How often did you think that your life makes sense / is meaningful during the last 4 weeks?	Never ☐	Rarely ☐	Often ☐	Always ☐
23) How often did you have problems to concentrate yourself during the last 4 weeks?	Never ☐	Rarely ☐	Often ☐	Always ☐
24) How often did you feel unsafe during the last 4 weeks?	Never ☐	Rarely ☐	Often ☐	Always ☐
25) How often did you have negative feelings, like anxiety, despair, sadness or depression during the last 4 weeks?	Never ☐	Rarely ☐	Often ☐	Always ☐

26) Did you suffer from physical pain, which prevented you from doing what you needed or wanted to do during the last 4 weeks?	No, never ☐	Yes, but rarely ☐	Yes, often ☐	Yes, always ☐
27) Did you suffer from physical pain when walking around during the last 4 weeks?	No, never ☐	Yes, but rarely ☐	Yes, often ☐	Yes, always ☐
28) Did you sleep well during the last 4 weeks?	No, never ☐	Yes, but rarely ☐	Yes, often ☐	Yes, always ☐
29) Did you have any problems to perform your daily living activities during the last 4 weeks?	No, never ☐	Yes, but rarely ☐	Yes, often ☐	Yes, always ☐

30) How would you rate your quality of life in general?	Very good ☐	Good ☐	Bad ☐	Very bad ☐

Thank you very much for your wonderful collaboration!!!

13.5.4. Supporting information. Table S1. Explanatory variables and indicators of the multivariable linear regression model at each step of the backward elimination procedure

Explanatory variables and indicators of the multivariable linear regression model	Full model		Step 1: eliminate age		Step 2: combine education		Step 3: combine education		Step 4: eliminate education	
	Coeff.	p-value	Coeff.	p-value	Coeff.	p-value	Coeff.	p-value	Coeff.	p-value
Sex[a]	-3.738	0.063	-3.717	0.064	-3.636	0.071	-3.388	0.089	-3.467	0.072
Age in years[b]	-0.025	0.721	---	---	---	---	---	---	---	---
Education: primary school[c]	1.169	0.638	1.298	0.596	1.233	0.618	0.355	0.871	---	---
Education: secondary school[c]	-1.639	0.569	-1.516	0.598	-1.119	0.694	---	---	---	---
Education: higher education[c]	3.558	0.552	3.901	0.510	---	---	---	---	---	---
Occupation: secondary sector[d]	5.990	0.198	5.884	0.205	5.860	0.208	6.255	0.177	6.272	0.176
Occupation: tertiary sector[d]	3.513	0.177	3.400	0.187	3.597	0.163	3.086	0.218	3.176	0.193
Wealth index[b]	1.201	0.044	1.198	0.045	1.288	0.029	1.227	0.036	1.242	0.030
S. haematobium infection of any intensity[e]	-3.903	0.557	-4.021	0.544	-3.827	0.564	-3.777	0.570	-3.760	0.572
S. mansoni infection of any intensity[f]	-16.314	0.017	-16.010	0.018	-16.725	0.014	-16.335	0.016	-16.428	0.015
Hookworm infection of any intensity[g]	-3.621	0.085	-3.651	0.082	-3.853	0.066	-3.933	0.061	-3.941	0.060
T. trichiura infection of any intensity[h]	-12.125	0.043	-12.089	0.043	-12.347	0.040	-12.441	0.038	-12.399	0.039
Plasmodium spp. infection of any intensity[i]	1.539	0.533	1.506	0.541	1.531	0.536	1.489	0.547	1.485	0.548
Constant	80.087	<0.001	78.895	<0.001	79.259	<0.001	79.210	<0.001	79.349	<0.001
Akaike information criterion of the model	1524.883	---	1523.007	---	1521.939	---	1520.571	---	1518.596	---
Likelihood ratio test p-value at this step	---	---	---	0.724	---	0.334	---	0.427	---	0.875

A multivariable linear regression model with a stepwise backward elimination procedure was adopted in order to identify those explanatory variables, which most significantly influence the study participants' quality of life scores. The data on socio-demographic factors, parasitology, and quality of life of the 187 study participants were collected in the Taabo health demographic surveillance system, south-central Côte d'Ivoire, in June 2010.

[a]Reference category: male. [b]Continuous variable. [c]Reference category: no education. [d]Reference category: primary sector. [e]Reference category: no *S. haematobium* infection. [f]Reference category: no *S. mansoni* infection. [g]Reference category: no hookworm infection. [h]Reference category: no *T. trichiura* infection. [i]Reference category: no *Plasmodium* spp. infection.

13.5.4. Supporting information. Table S1. Continued

Explanatory variables and indicators of the multivariable linear regression model	Step 5: eliminate *S. haematobium*		Step 6: eliminate *Plasmodium* spp.		Step 7: combine occupation		Final model (see also Table 5)	
	Coeff.	p-value	Coeff.	p-value	Coeff.	p-value	Coeff.	p-value
Sex[a]	-3.551	0.065	-3.575	0.064	-3.528	0.067	-3.528	0.067
Age in years[b]	---	---	---	---	---	---	---	---
Education: primary school[c]	---	---	---	---	---	---	---	---
Education: secondary school[c]	---	---	---	---	---	---	---	---
Education: higher education[c]	---	---	---	---	---	---	---	---
Occupation: secondary sector[d]	6.003	0.193	6.189	0.179	3.811	0.094	3.811	0.094
Occupation: tertiary sector[d]	3.265	0.179	3.300	0.175	---	---	---	---
Wealth index[b]	1.267	0.027	1.249	0.029	1.207	0.034	1.207	0.034
S. haematobium infection of any intensity[e]	---	---	---	---	---	---	---	---
S. mansoni infection of any intensity[f]	-17.153	0.009	-17.077	0.009	-16.420	0.011	-16.420	0.011
Hookworm infection of any intensity[g]	-3.972	0.058	-3.925	0.061	-3.932	0.061	-3.932	0.061
T. trichiura infection of any intensity[h]	-12.423	0.038	-12.682	0.034	-12.623	0.035	-12.623	0.035
Plasmodium spp. infection of any intensity[i]	1.452	0.557	---	---	---	---	---	---
Constant	79.378	<0.001	79.858	<0.001	79.721	<0.001	79.721	<0.001
Akaike information criterion of the model	1516.910	---	1515.253	---	1513.606	---	1513.606	---
Likelihood ratio test p-value at this step	---	0.575	---	0.558	---	0.553	---	0.553

A multivariable linear regression model with a stepwise backward elimination procedure was adopted in order to identify those explanatory variables, which most significantly influence the study participants' quality of life scores. The data on socio-demographic factors, parasitology, and quality of life of the 187 study participants were collected in the Taabo health demographic surveillance system, south-central Côte d'Ivoire, in June 2010. [a]Reference category: male. [b]Continuous variable. [c]Reference category: no education. [d]Reference category: primary sector. [e]Reference category: no *S. haematobium* infection. [f]Reference category: no *S. mansoni* infection. [g]Reference category: no hookworm infection. [h]Reference category: no *T. trichiura* infection. [i]Reference category: no *Plasmodium* spp. infection.

13.6. Scope and limits of an anamnestic questionnaire in a control-induced low-endemicity helminthiasis setting in south-central Côte d'Ivoire

13.6.1. Supporting information. Text S1. Questionnaire for evaluating the health state of individuals in June 2010 in the Taabo health demographic surveillance system, south-central Côte d'Ivoire (in French)

Enquête pour évaluer l'état de santé

Questionnaire pour les participents à l'enquête transversal au SSD de Taabo en Juin 2010.

Cher(e) participant(e),

Nous avons rédigé quelques questions concernant votre avis sur votre état de santé et vos activités quotidiennes. Ces questions ne sont pas un test avec des bonnes et des mauvaises réponses. Pour nous, il est plus important de savoir comment vous allez et seule votre opinion personnelle et honnête nous intéresse. Nous vous prions donc de nous aider à remplir le questionnaire complètement.

Village/Campement :								
Date :	**Nom de l'enquêteur :**							
Numéro d'identification du participant								

Facteur de risque (6)
Indiquez le numéro correct (1, 2 ou 9) pour chaque réponse prévue à la gauche.

1) Quelles activités liées à l'eau (de rivières, lacs, marigot etc.) avez-vous pratiqué durant ces 4 dernières semaines ? (1=oui / 2=non / 9=ne sait pas)	faire la lessive	___
	faire la vaisselle	___
	se laver	___
	nager	___
	cuisiner	___
	laver les enfants	___
	traverser les rivières	___
	pêcher au filet	___
	pêcher à l'hameçon	___
	cultiver du riz	___
	pratiques religieuses	___
	autres :……..	___
2) Quelle eau buvez-vous ? (1=oui / 2=non / 9=ne sait pas)	eau de marigot, ruisseau, rivière	___
	eau de pluie	___
	eau courrant / robinet	___
	eau en bouteille / eau minérale / awa	___
	autres :……..	___
3) Ces 4 dernières semaines, avez-vous utilisé…		___ ___ ___ ___

(1=oui / 2=non / 9=ne sait pas)	une moustiquaire	
	des insecticides (p. ex. timor)	
	moustico	
	autres :……..	
4) Est-ce que vous utilisez du savon pour…	faire la lessive	___
(1=oui / 2=non / 9=ne sait pas)	faire la vaisselle	___
	vous laver	___
	vous laver les mains avant de manger	___
	vous laver les mains après les selles	___
	laver les mains au retour du travail	
5) De temps en temps, mangez-vous…	de la viande crue	___
(1=oui / 2=non / 9=ne sait pas)	des poisons crus	___
	des fruits crus	___
	des légumes crus	___
6) Quels animaux possédez-vous ?	chien	___
(1=oui / 2=non / 9=ne sait pas)	poule / volaille	___
	lapin	___
	cobaye	___
	cochon	___
	cabri	___
	mouton	___
	vache / buffle	___
	autres :……	___

Signes & Symptômes (2)

7) Avez-vous expérimenté un ou plusieurs signes ou symptômes suivants durant ces 4 dernières semaines?	sang dans les selles	____
(1=oui / 2=non / 9=ne sait pas)	sang dans l'urine	____
	mal de ventre	____
	ballonnement du ventre	____
	perte de l'appétit	____
	mal de tête	____
	troubles visuels	____
	problème pour articuler/ parler	____
	fièvre/ corps qui chauffe	____
	faiblesse/ fatigue	____
	vomissement	____
	vertige	____
	diarrhée	____
	douleur en pissant	____
	perte de poids	____
	boutons ou tache sur la peau	____
	mal à la poitrine	____
	problème pour respirer	____
	toux	____
	corps qui gratte	____
	partie du corps enflée	____
	mal de rein	____
	autres :……..	____

8) Quelles sont les maladies fréquentes dans votre ménage ? (1=oui / 2=non / 9= ne sait pas)	Bilharziose ou schistosomiase	
	Tuberculose	
	Diarrhée	
	Onchocercose	
	VIH / SIDA	
	Méningite	
	Filariose / éléphantiasis	
	Paludisme	
	Ulcère de buruli	
	Vers intestinaux	
	Lèpre	
	Je ne connais pas ces maladies	

Qualité de vie (adultes : WHOQOL bref (24))
Marquez la réponse qui est la plus vraie pour chaque question.

9) Vous sentez-vous en bonne santé ?	Non, pas du tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
10) Avez vous eu assez d'énergie durant ces 4 dernières semaines pour mener votre vie quotidienne ?	Non, pas du tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
11) Avez-vous eu assez d'argent pour acheter tout ce dont vous aviez besoin durant ces 4 dernières semaines ?	Non, pas du tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
12) Avez-vous eu assez de temps libre durant ces 4 dernières semaines ?	Non, pas du tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
13) Êtes-vous satisfait de votre capacité de travail ?	Non, pas du tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
14) Êtes-vous satisfait de vos relations personnelles (par exemple avec vos amis ou votre famille) ?	Non, pas de tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
15) Êtes-vous satisfait du support de vos amis ?	Non, pas de tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
16) Êtes-vous satisfait de votre logement ?	Non, pas de tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
17) Êtes-vous satisfait de votre accès au centre de santé le plus proche ?	Non, pas de tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐
18) Êtes-vous satisfait de vos possibilités de transport ?	Non, pas de tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐

19) Êtes-vous content avec vous et votre situation en générale ?	Non, pas de tout ☐	Plus ou moins ☐	Oui, la plupart du temps ☐	Oui, absolument ☐

20) Combien de fois avez-vous pris des médicaments durant ces 4 dernières semaines ?	Jamais ☐	Rarement ☐	Souvent ☐	Toujours ☐
21) Combien de fois vous êtes-vous réjouit de votre vie durant ces 4 dernières semaines?	Jamais ☐	Rarement ☐	Souvent ☐	Toujours ☐
22) Combien de fois avez-vous pensé que votre vie avait un sens durant ces 4 dernières semaines?	Jamais ☐	Rarement ☐	Souvent ☐	Toujours ☐
23) Combien de fois avez-vous eu des problèmes pour vous concentrer durant ces 4 dernières semaines ?	Jamais ☐	Rarement ☐	Souvent ☐	Toujours ☐
24) Combien de fois ne vous êtes vous pas sentis en sécurité durant ces 4 dernières semaines?	Jamais ☐	Rarement ☐	Souvent ☐	Toujours ☐
25) Combien de fois avez-vous eu des sentiments négatifs, comme par exemple la peur, le désespoir, la tristesse ou la dépression ?	Jamais ☐	Rarement ☐	Souvent ☐	Toujours ☐

26) Avez vous souffert de douleurs, durant ces 4 dernières semaines, qui vous ont handicapées dans vos activités quotidiennes ?	Non, jamais ☐	Oui, mais rarement ☐	Oui, souvent ☐	Oui, toujours ☐
27) Avez-vous eu de la peine à marcher durant ces 4 dernières semaines?	Non, jamais ☐	Oui, mais rarement ☐	Oui, souvent ☐	Oui, toujours ☐
28) Avez-vous bien dormi durant ces 4 dernières semaines?	Non, jamais ☐	Oui, mais rarement ☐	Oui, souvent ☐	Oui, toujours ☐
29) Avez-vous eu des problèmes pour exécuter vos activités quotidiennes durant ces 4 dernières semaines?	Non, jamais ☐	Oui, mais rarement ☐	Oui, souvent ☐	Oui, toujours ☐

30) Comment jugez-vous votre qualité de vie, en général ?	Très bien ☐	Bien ☐	Mal ☐	Très mal ☐

Merci beaucoup de votre merveilleuse collaboration!!!