2020-2022

IRCCS - SACRO CUORE DON CALABRIA

Research

ACTIVITY REPORT

VIA DON A. SEMPREBONI, 5 – 37024 NEGRAR DI VALPOLICELLA (VERONA) | TEL. +39 045 60.13.111

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Istituto Sacro Cuore Don Calabria - Irccs malattie infettive e tropicali
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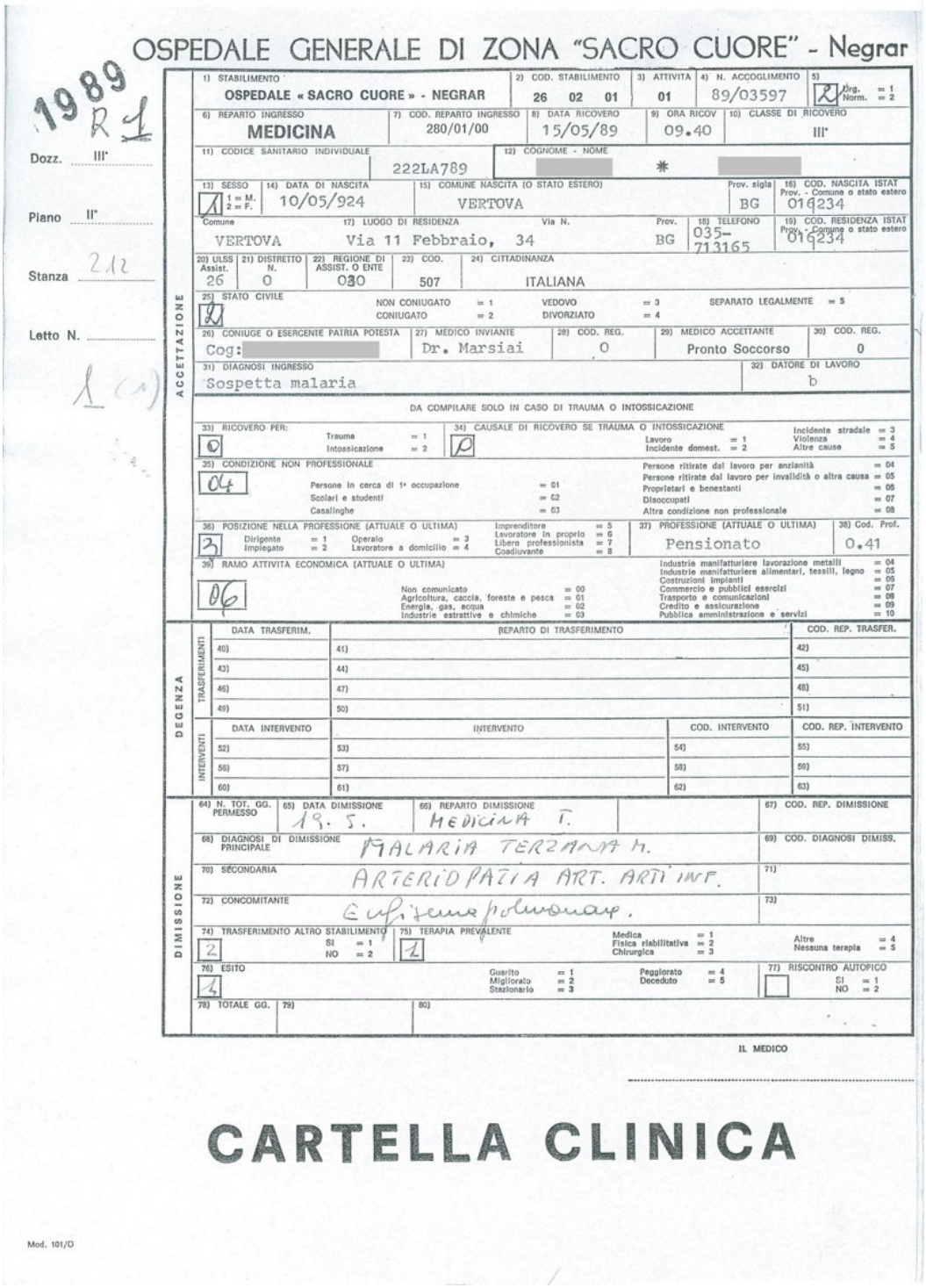


OSPEDALE GENERALE DI ZONA "SACRO CUORE" - Negrar

1989 R 1

Dozz. III°

Piano II°

Stanza 212

Letto N.

1 (1)

ACCETTAZIONE

1) STABILIMENTO: OSPEDALE « SACRO CUORE » - NEGRAR | 2) COD. STABILIMENTO: 26 02 01 | 3) ATTIVITÀ: 01 | 4) N. ACCOGLIMENTO: 89/03597 | 5) Urg. = 1 Norm. = 2: 2

6) REPARTO INGRESSO: MEDICINA | 7) COD. REPARTO INGRESSO: 280/01/00 | 8) DATA RICOVERO: 15/05/89 | 9) ORA RICOV: 09.40 | 10) CLASSE DI RICOVERO: III°

11) CODICE SANITARIO INDIVIDUALE: 222LA789 | 12) COGNOME - NOME: [redacted] *

13) SESSO (1 = M. 2 = F.): 1 | 14) DATA DI NASCITA: 10/05/924 | 15) COMUNE NASCITA (O STATO ESTERO): VERTOVA | Prov. sigla: BG | 16) COD. NASCITA ISTAT Prov. - Comune o stato estero: 016234

17) LUOGO DI RESIDENZA — Comune: VERTOVA | Via N.: Via 11 Febbraio, 34 | Prov.: BG | 18) TELEFONO: 035-713165 | 19) COD. RESIDENZA ISTAT Prov. - Comune o stato estero: 016234

20) ULSS Assist.: 26 | 21) DISTRETTO N.: 0 | 22) REGIONE DI ASSIST. O ENTE: 030 | 23) COD.: 507 | 24) CITTADINANZA: ITALIANA

25) STATO CIVILE: 2 (NON CONIUGATO = 1, CONIUGATO = 2, VEDOVO = 3, DIVORZIATO = 4, SEPARATO LEGALMENTE = 5)

26) CONIUGE O ESERCENTE PATRIA POTESTÀ: Cog: [redacted] | 27) MEDICO INVIANTE: Dr. Marsiai | 28) COD. REG.: 0 | 29) MEDICO ACCETTANTE: Pronto Soccorso | 30) COD. REG.: 0

31) DIAGNOSI INGRESSO: Sospetta malaria | 32) DATORE DI LAVORO: b

DA COMPILARE SOLO IN CASO DI TRAUMA O INTOSSICAZIONE

33) RICOVERO PER: 0 (Trauma = 1, Intossicazione = 2) | 34) CAUSALE DI RICOVERO SE TRAUMA O INTOSSICAZIONE: 0 (Lavoro = 1, Incidente domest. = 2, Incidente stradale = 3, Violenza = 4, Altre cause = 5)

35) CONDIZIONE NON PROFESSIONALE: 04 (Persone in cerca di 1ª occupazione = 01, Scolari e studenti = 02, Casalinghe = 03, Persone ritirate dal lavoro per anzianità = 04, Persone ritirate dal lavoro per invalidità o altra causa = 05, Proprietari e benestanti = 06, Disoccupati = 07, Altra condizione non professionale = 08)

36) POSIZIONE NELLA PROFESSIONE (ATTUALE O ULTIMA): 3 (Dirigente = 1, Impiegato = 2, Operaio = 3, Lavoratore a domicilio = 4, Imprenditore = 5, Lavoratore in proprio = 6, Libero professionista = 7, Coadiuvante = 8) | 37) PROFESSIONE (ATTUALE O ULTIMA): Pensionato | 38) Cod. Prof.: 0.41

39) RAMO ATTIVITÀ ECONOMICA (ATTUALE O ULTIMA): 06 (Non comunicato = 00, Agricoltura, caccia, foreste e pesca = 01, Energia, gas, acqua = 02, Industrie estrattive e chimiche = 03, Industrie manifatturiere lavorazione metalli = 04, Industrie manifatturiere alimentari, tessili, legno = 05, Costruzioni impianti = 06, Commercio e pubblici esercizi = 07, Trasporto e comunicazioni = 08, Credito e assicurazione = 09, Pubblica amministrazione e servizi = 10)

DEGENZA

TRASFERIMENTI

DATA TRASFERIM.	REPARTO DI TRASFERIMENTO	COD. REP. TRASFER.
40)	41)	42)
43)	44)	45)
46)	47)	48)
49)	50)	51)

INTERVENTI

DATA INTERVENTO	INTERVENTO	COD. INTERVENTO	COD. REP. INTERVENTO
52)	53)	54)	55)
56)	57)	58)	59)
60)	61)	62)	63)

DIMISSIONE

64) N. TOT. GG. PERMESSO | 65) DATA DIMISSIONE: 19. 5. | 66) REPARTO DIMISSIONE: MEDICINA T. | 67) COD. REP. DIMISSIONE

68) DIAGNOSI DI DIMISSIONE PRINCIPALE: MALARIA TERZANA M. | 69) COD. DIAGNOSI DIMISS.

70) SECONDARIA: ARTERIOPATIA ART. ARTI INF. | 71)

72) CONCOMITANTE: Enfisema polmonare. | 73)

74) TRASFERIMENTO ALTRO STABILIMENTO (SI = 1, NO = 2): 2 | 75) TERAPIA PREVALENTE: 1 (Medica = 1, Fisica riabilitativa = 2, Chirurgica = 3, Altre = 4, Nessuna terapia = 5)

76) ESITO: 1 (Guarito = 1, Migliorato = 2, Stazionario = 3, Peggiorato = 4, Deceduto = 5) | 77) RISCONTRO AUTOPICO (SI = 1, NO = 2):

78) TOTALE GG. | 79) | 80)

IL MEDICO

CARTELLA CLINICA

Mod. 101/O

The medical record of the first patient admitted to the Centre for Tropical Diseases at Negrar hospital, May 1989

Introduction

By Zeno Bisoffi, scientific director

Being (for reasons of age) in some ways the historical memory of the Centre for Tropical Diseases, now DITM, I thought I would briefly summarize the path that has brought us to this point.

The "Vision"

The IRCCS was born in a hospital guided by St. Giovanni Calabria's constantly repeated principle: "The sick person, after God, is our true master", and by its constant focus on the "last ones". Our vision, irrespective of the religious denomination professed or not, is rooted precisely in this phrase, and it is expressed in the right to quality care for all, regardless of income and nationality. A right that is also clearly outlined by the Italian Constitution.

The very first core of the Sacro Cuore Hospital, 1920s

Dealing specifically with tropical diseases has put us at the centre of this vision, since we are dealing by definition with the diseases of the poor, the neglected and forgotten. Neglected, them and their diseases, even by research. In all these years, we have mainly worked with "neglected and forgotten" patients. Therefore, also research activities, not just care activities, should be ultimately guided by this 'vision'. Research is neither aseptic nor 'neutral'; this obviously applies to applied and translational research, but also to fundamental research.

The Mission

The centre, currently Department of Infectious, Tropical Diseases and Microbiology (DITM), finds its Mission in the four objectives with which it was founded in 1988:

1. Carry out activities for the diagnosis and treatment of tropical diseases

2. Develop research activities in the clinical, parasitological and epidemiological fields

3. Promote the training and professional upgrading of health professionals

4. Implementing information activities for the prevention of travellers' diseases.

I would like to emphasize the foresight of our founders, at a time when research was certainly not among the main activities of our hospital. In fact, in the history of the centre, the research objective is the last one to have materialized, with a volume of activity that is still very modest since it is a very small centre, but which has grown steadily over time. In particular, as far as research is concerned, the mission includes a number of fundamental themes:

Research is rooted in our vision, so its ultimate aim is to make its contribution to finding scientifically based solutions to improve access to quality care, particularly for neglected and poverty-related diseases, or rather, for underprivileged populations, both in Italy (in particular among immigrants) and in the countries where these diseases are most prevalent;

Our area of recognition, the one for which we are evaluated and funded by the Ministry of Health, is on infectious and tropical diseases: therefore non-tropical infectious diseases are also part of the mission. But our tradition and focus can only remain anchored to our core business', which has not changed.

Applied and translational research is directly aimed at finding methods and solutions (therapies; diagnostic tools; strategies) first and foremost through the rigorous evaluation of existing ones; however, the possible contribution to innovative solutions and methods is not neglected;

Hence the importance of the field of biomedical research, including the various 'omics', the search for new diagnostic and prognostic biomarkers, cell cultures, in particular to improve knowledge of emerging pathogens (viral and otherwise).

Networks. No research centre, let alone one as small as ours, can think of being autonomous and self-sufficient. Collaborations and networks are fundamental and often their value is greater than the sum of their individual contributions. The acti-

ve presence in networks, whether national, European or international, with centres that share at least in part of our ideal vision, has been sought since the dawn of our history and must grow steadily.

A short history – key milestones

At the end of the 1980s, a Brother of the Opera Don Calabria, Giuseppe Brunelli, then one of the Board of Directors of the Sacro Cuore - Don Calabria Hospital in Negrar, in the province of Verona, had the bizarre idea of setting up a Foundation for Tropical Diseases in the heart of Valpolicella and Amarone vineyards. At the time, there were no centres of this type in Italy, and very few in Europe. The Foundation was officially established on 23 March 1988, and the symbolic foundation stone was blessed less than a month later (17 April) by Pope John Paul II, who was visiting the hospital. The aims declared in the first statute, as above mentioned, were very ambitious: diagnosis and treatment of tropical diseases, research activities in the clinical, parasitological and epidemiological fields, training of health professionals, providing information for the prevention of travellers' diseases.

To respond to these aims, two new operational units were set up the following year at the hospital in Negrar: the Centre for Tropical Diseases - CTD (diagnosis and treatment ward and outpatient clinic) and the Service of Epidemiology and Laboratory for Tropical Diseases. Mario Marsiaj, a physician with extensive clinical experience in Uganda, was called to head the CTD. The late Maria Luisa Ricciardi, a great parasitologist, then retired, was asked to set up the parasitology lab.

The first patient was admitted at the CTD on May 15th 1989, a case of *P. falciparum* malaria. Less than ten month later, I joined the medical team, that included, besides Marsiaj, the infectivologist Pierangelo Rovere. The ward was a corridor on the second floor of the old hospital, where, in a small room, there was also a mini laboratory, with a microscope and little more. The first few months, however, the activity was mainly outpatient and a large part consisted of consultations, mainly by telephone, to travellers. The ward was often empty, or almost. Over the months and years, the caseload increased rapidly, both for the ward and the laboratory. Malaria cases in particular were relatively numerous, due to the temporal coincidence with the first waves of immigrants, to the relatively high numbers of missionaries, aid workers and other expatriates, and because of the diagnostic accuracy that, thanks to Ricciardi's teachings, ensured that the diagnosis was never missed, even for low parasite loads.

Our pride in the quality of microscopic diagnosis of malaria (and more) was abruptly wounded in 1993, when the Reference Parasitology Laboratory of the Istituto Superiore di Sanità (ISS) in Rome (director the late Giancarlo Majori) challenged two of our diagnoses. Urged by Ricciardi, we (Mario and myself) shortly embarked on our

march on Rome! Already belligerent and ready for battle, we were actually welcomed at the ISS by people just as enthusiastic as we were (in addition to G. Majori, his deputy Guido Sabatinelli). Our march on Rome thus became the first step in a long friendship and collaboration with the people I have mentioned, and others, mostly under the umbrella of the Italian Society of Tropical Medicine (SIMET), and also the first tangible proof of something that has been amply confirmed over time, namely that particularly passionate people are found in the world of parasitology and tropical medicine. These new friends encouraged us to start publishing, given our already rich case record: something we practitioners had scarcely considered until then.

In the same year 1993, on the initiative of Mario Marsiaj and other enlightened persons, the CESAIM was founded in Verona, an outpatient clinic for undocumented immigrants that quickly became one of the first in Italy in terms of the number of patients examined, and that still maintains a close collaboration with the CTD (now DITM).

In June, 1994 we presented our first abstracts at a congress: this was the National Congress of the Italian Society of Parasitology (SOIPA) in Ozzano Emilia, near Bologna, followed in October, 1995, by the first National Congress of SIMET (Mondello, Palermo). In the same year we also presented a few abstracts at the first ECTMIH (European Congress of Tropical Medicine and Hygiene, in Hamburg) and so we began, also with the first very sporadic publications in peer-reviewed journals, to (very modestly) address the Foundation's second objective.

April 17th, 1988: Pope John Paul II, visiting the Negrar hospital, blesses the foundation stone of the center for tropical Diseases

Also in 1995, the first residential course was held from 7 to 10 December: Clinical Logic in Tropical Medicine, with Prof. Jef Van den Ende from Antwerp (with whom the

collaboration would continue for a quarter of century), with this we also began to respond to the third objective, with the courses that later became traditional; the mentioned Clinical Logic, the course on Basic Laboratory for Tropical Countries, and others, also starting a collaboration with the University of Brescia that would be then extended to the University of Florence and leading, years later, to the Italian Master on Tropical Medicine and Global Health.

In March 1996, our hospital was one of the founding partners of CECOMET (Centro de Epidemiologia Comunitaria y Medicina Tropical) in Esmeraldas, Ecuador, a collaboration strongly desired and promoted by Mariella Anselmi, later one of the CTD's doctors, and directed for many years by Juan Moreira, a great researcher and dear friend who sadly passed away on 14 July 2014.

In the meantime, the laboratory consolidated itself with the introduction of methods other than the classic ones for parasite research, such as serology for the main parasitic infections and antigen testing. It also collaborated in setting up new laboratories in low-middle-income countries (LMIC), e.g. in Ecuador and Angola.

In 1998, a Milestone for the CTD: the 2nd National Congress of SIMET (from 7 to 9 May), which we organized in Bardolino, near Verona, was a success, with over 600 participants and the beginning of an even closer collaboration with SIMET.

At the end of the same year Mario Marsiaj retired early, to be able to return to collaborate directly with the small hospital of Angal, in Uganda, as he continues to do today at the age of 87.

In 1999, we were founding members of the European network TropNetEurop (now TropNet).

That same year, the CTD also began to function fully as a travel medicine centre, with the opening of the outpatient clinic for international prophylaxis and vaccinations, thus fulfilling the Foundation's fourth objective and becoming the first hospital in Italy to manage the entire cycle of travel medicine, from pre-departure prophylaxis and counselling to outpatient or hospital management of clinical cases on return.

In September 2000, and again in 2005, the European Course on Tropical Epidemiology (ECTE), a three-week intensive annual course, the result of a collaboration between European tropical medicine centres and institutes, was organized by the CTD and held in Negrar.

In the first decade of the new millennium, cooperation initiatives with low-middle-income countries (LMIC) were consolidated (such as with Ecuador - CECOMET) and/or launched (e.g. with Burkina Faso), also including a translational research component.

In 2009, another Milestone: the European Congress of Tropical Medicine and Hygiene (ECTMIH) was organized by the CTD on behalf of SIMET and held (for the first time in Italy), in Verona (Gran Guardia Palace), from 6 to 10 September. The central theme of the congress was: Equity, human rights and access to care. In addition to the classic scientific sessions, the congress also had two evenings open to citizens, with a well-attended debate on migration issues.

Further collaborations ensued from ECTMIH, including the participation, for the first time for the CTD, in a European project (COHEMI), 2011-2013, on the health of Latin American migrants. The project was coordinated by the Mario Negri Institute of Milan, in partnership with the Clinic of Infectious and Tropical Diseases in Florence, the CRESIB in Barcelona (now ISGLOBAL), the CECOMET and others. This was a further example showing that networks and collaborations are crucial.

In 2013, the CTD was officially designated by the Veneto Region as Regional Reference Centre for Tropical Diseases, and in the same year the laboratory was further developed with the introduction of molecular biology techniques to further increase the accuracy of routine parasitological diagnostics, and also as a support for research. CTD became the first and only centre in Italy to introduce molecular biology in the diagnostic routine for parasitic infections. This consolidated the recognized role of the CTD, with the parasitology laboratory (SAELMT), as a leading hospital centre for human parasitology in the country.

In 2014, another Milestone: an international meeting was organized in the occasion of the CTD's 25th anniversary, titled "From Tropical Diseases to Global Health" (16th to 18th September, 2014), indicating somehow the new, broadened perspective of our activity and our mission.

At that time, however, none of us imagined that the second 25 years of our history would open with a totally unexpected challenge: the path, which began immediately afterwards, prompted by the hospital management, to obtain recognition as an IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico - Institute for Hospitalization and Treatment of a Scientific Character) for our discipline.

For the first time, we were set (very ambitious) goals to achieve in the field of research. Up until then, research had been a sporadic activity developed for our own personal interest in investigating topics related to clinical activity, or to collaboration with tropical countries (such as the aforementioned Ecuador and Burkina Faso). Translational research, aimed at solving concrete problems for the benefit of patients or populations: evaluation of the accuracy of diagnostic tests, description of clinical cases of particular interest, study of the best treatment options. The number of publications in peer reviewed journals had indeed increased over time, from just 5 articles in the 1990-2000 decade to over 50 in the following one, but our scienti-

fic output was still light years away from the (very demanding) requirements of an IRCCS. Suddenly, research became a main focus of our activities, thus reshaping our perspective. The second twenty-five years began with an apparently prohibitive challenge, considering our limited size compared to the existing IRCCSs, of which only one was for infectious diseases, the INMI Spallanzani in Rome. The challenge involved first of all a strengthening of our team, medical, biological and of support, which thanks to a (not easy but effective) dealing with the hospital management was partially achieved in a relatively short time.

The Veneto Region approved the proposal and already a few months later, on 15 April 2015, sent the Ministry a formal request for recognition of our hospital as an IRCCS for tropical diseases and migration medicine.

The request was based on what had always been our strengths, both as clinical and diagnostic activities and as research. It must be said, however, that over the years, non-tropical infectious diseases had also become an increasingly significant component of our clinical caseload. On 26 May 2016, the first site visit of the commission sent by the Directorate General for Research of the Ministry of Health to evaluate the request took place. The commission, while evaluating very positively the overall activity of the hospital and of the CTD, which in the meantime had become (as of 1 December 2015) Department of Infectious, Tropical Diseases and Microbiology (DITM), considered that the requirements for recognition were not yet fully met and indicated some suggestions, including that of modifying the request for the discipline of recognition to Infectious and Tropical Diseases and to further strengthen the research team.

A clinical research unit on infectious and tropical diseases, led by Dora Buonfrate, and a biomedical research unit, led by Chiara Piubelli, were created, and the number of professionals, both in the clinical and laboratory sectors, was significantly increased in a short time, even though our size remained tiny, even if compared to the smallest IRCCSs.

Another Milestone: following the ministerial commission's second visit of January 10th, 2018, by decree of the Minister of Health of 23rd May, 2018, the Sacro Cuore Don Calabria Hospital was formally recognized as an Institute for Hospitalization and Treatment with Scientific Character (IRCCS) for the discipline of infectious and tropical diseases.

This apparent point of arrival was actually the starting point of a new challenge. Research became to all intents and purposes a main focus, alongside clinical and diagnostic activity. Ours was, in terms of size and number of researchers, the smallest of the over 50 IRCCS, and maintaining the recognition was an equally great challenge.

No one could have foreseen that the COVID-19 tsunami would soon overwhelm the planet, and consequently also our hospital. In addition to putting a very hard physical, moral and psychological strain on our medical team led by Andrea Angheben, at the forefront of this momentous challenge, and on the microbiology team led by Francesca Perandin, this tsunami could have brought down our new-born IRCCS, had we not from the very beginning set ourselves the objective, shared by most, that research should not be abandoned, overwhelmed by the primary need to treat the patients. In retrospect, after more than two, very hard years, we can say that IRCCS recognition and the consequent strengthening of the team already underway, and continued during the pandemic, made it possible, on the one hand, to deal with it more effectively, and on the other, not to suspend research activity, and indeed to increase it, first and foremost with numerous studies on, precisely, COVID-19. This is not to say that the tsunami has not left deep wounds, some difficult to heal.

The new high-biocontainment BSL-2/BSL-3 virology lab established in 2022

In the midst of the pandemic, came the expected, new visit, this time remotely, of the ministerial commission for the confirmation of IRCCS recognition. The visit took place on 18 January 2021, the outcome was fully positive, and the subsequent Ministerial Decree of 27 July confirmed the scientific character of the institute.

In the same year, a few months later, a further Milestone. On 8th October, on the occasion of the annual feast of San Giovanni Calabria, the new BSL2 - BSL3 laboratory for cell cultures and virology was inaugurated, entrusted to Concetta Castilletti, one of Italy's best virologists, who had joined the DITM coming from INMI Spallanzani.

The last two years saw a further intensification of research activities, together with the new, difficult challenge of meeting the increasingly demanding targets set by the Ministry. In the meantime, as of 1/7/2022, the direction of the DITM passed to Federico Gobbi, who would also become Associate Professor of Infectious and Tropical Diseases at the University of Brescia a few months later, and who in recent years has been working intensively, together with Concetta Castilletti and other colleagues, to intensify training and research activities in LMICs, starting from Angola where there is an Opera Don Calabria hospital.

A history of almost 35 years, summed up in a few pages, ideally handing over the witness to my younger colleagues. Many of them, and hopefully many more, will still be on board in May 2039 to duly celebrate our centre's 50 years of activity. If I am still alive, I hope they will invite me.

IRCCS Sacro Cuore Don Calabria activities in Angola

Since 1994, the Congregazione Poveri Servi della Divina Provvidenza (CPSDP)/IRCCS Sacro Cuore Don Calabria Hospital, with the support of the NGO Unione Medico Missionaria Italiana (UMMI), has been managing the Hospital Divina Providência (HDP), a hospital complex that provides basic health services through a referral hospital and five peripheral Health Centres, in the Municipality of Kilamba Kiaxi. Thanks to the collaboration with Eni Spa, since 1999 this presence has been gradually strengthened, first, in 2000 with the addition of a new paediatric unit, and then, in 2009, with the empowerment of services for the maternal and child population of the Municipality of Kilamba Kiaxi through a wide array of services, such as construction and development of new health services, technical training of staff, and the promotion of community health. Thanks to these developments, the HDP has been able to activate a national reference centre for the fight against malnutrition, which has been added to the other two reference centres for the treatment of tuberculosis and of patients with HIV/AIDS. Since 2013, the partnership between Eni Spa and the ODP has been further consolidated in the area of training, promoting ongoing training programmes aimed not only at HDP health workers, but also extended to the entire Province of Luanda.

Today, all IRCCS projects in Angola are part of a broad development framework that aims to be sustainable and long-lasting, with three arms: training, care, and research. An example of this integrated approach was implemented with a training module on HIV. An international lecturer from the University of Turin, Italy, conducted two training modules on the subject, respectively for doctors and nurses, participating in the clinical activity and assisting doctors and nurses in running the HIV clinic. At the same time, care activities were enhanced by sending infectious disease trainees from abroad to HDP for further support; and finally, data on the access of HIV patients before and during the COVID-19 pandemic were collected for research activities and a scientific publication. The current training framework includes 54 such training modules for doctors, nurses and laboratory technicians, covering infectious diseases (HIV, tuberculosis, neglected tropical diseases), epidemiological surveillance, clinical logic, infectious diseases ecography, diagnostics in parasitology, women's and children's health). The courses are fully embedded in the clinical context of the hospital, so that lecturers can interact with hospital's doctors and nurses, supporting and enhancing routine clinical practice and research activity at the same time, according to the principle of translational research, rapidly transferable from the laboratory to the patient's bedside.

February 6, 2019: the President of the Italian Republic Sergio Mattarella visits the Hospital Divina Providência in Luanda, Angola

The current scientific activity has two main objectives. The first is to 'take a snapshot' of the current epidemiological situation in order to obtain updated data and propose solutions for any problems encountered. The second objective concerns the study

of the 'referencia' and 'contra-referencia' process in the Kilamba-Kiaxi district and the description of the local epidemiological framework. The research projects were entrusted to an Angolan university professor of paediatrics, who is well acquainted with the reality of Luanda. On the basis of the data emerging from this research, it will be possible to assess whether the pyramid system currently used (peripheral health centres, first-, second- and third-level hospitals) is optimal for the Kilamba Kiaxi district, or whether other models could be adopted: for example, the Hospital Divina Providencia, although itself a first level hospital, could be considered a 'referencia' for HIV, tuberculosis and malnutrition.

In addition to close collaboration with the health staff of hospitals and peripheral centres, in order to fully integrate the research projects into the local context, close collaboration with INIS (Istituto Nacional de Saude Pubblica), the Angolan Ministry of Health, and the University of Medicine of Luanda is of paramount importance. Partnering with these institutions will make it possible for Angolan health personnel eager to train and implement their research skills to attend the Divina Providencia Hospital. In addition, the support of international institutions of excellence, besides guaranteeing a high level of training, will facilitate the possibility of internships at the HDP for personnel from Europe and South America, fostering relations between Angolan and foreign health personnel in an atmosphere of mutual scientific growth and enrichment.

There are several other projects specifically inside the HDP, in order to strengthen the health activity on site and the attractiveness for specialised personnel. These include:

the establishment of a Training and Clinical Research Centre where trainee and specialised health personnel, both Angolan and expatriate, can find a suitable environment to receive adequate training, provide high-level health care and develop research projects.

the creation of a Microbiology Laboratory, including virology, bacteriology and parasitology, which can provide health personnel with microbiological diagnostic possibilities that are currently unavailable, and facilitate the implementation of research projects.

'Luanda Cardiac Surgery'. The IRCCS of Negrar, in collaboration with the Divina Providencia Hospital, will provide support for the control of hospital infections at the former Sanatorium hospital, providing medical and microbiological advice and thus strengthening relations with Angolan and Italian institutions (Monzino Cardiac Surgery Centre in Milan).

Cabinda' project, which involves a support project for the Hospital Geral in Cabinda,

about an hour's flight north of Luanda, for the management of hospital infections and the development of a malaria training, assistance and research programme with peripheral health centres, providing the latter with microscopes, slides and stains for microscopy examinations, rapid tests and medical/logistical support. Subsequent research programmes can then be extended to other infectious diseases (dengue and other arboviruses, schistosomiasis, etc.), and, above all, research projects can be drawn up for the management of fevers (malarial and non-malarial), which are extremely important for health personnel in peripheral areas.

The IRCCS in a nutshell

The number of medical and biomedical researchers has grown significantly from 2017 (the last year before recognition by the Ministry of Health) to 2020, but has remained essentially stable over the last three years, and so has the number of research support staff (Figures 1 and 2). In both groups, women predominate (Figure 3). Among the researchers, four have obtained academic qualification (two as full professors and two as associate professors, one of whom, Prof. Federico Gobbi, lectures at the University of Brescia, in convention with our IRCCS).

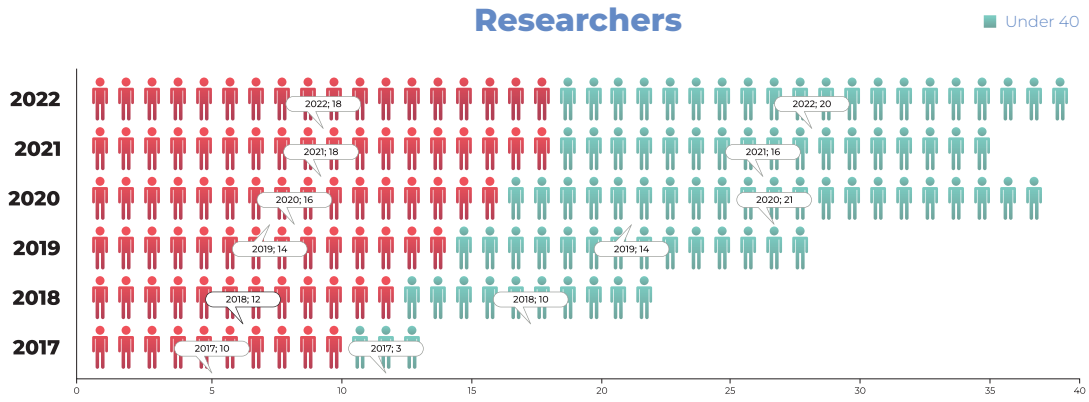


Fig. 1: number of researchers (biologists and physicians)

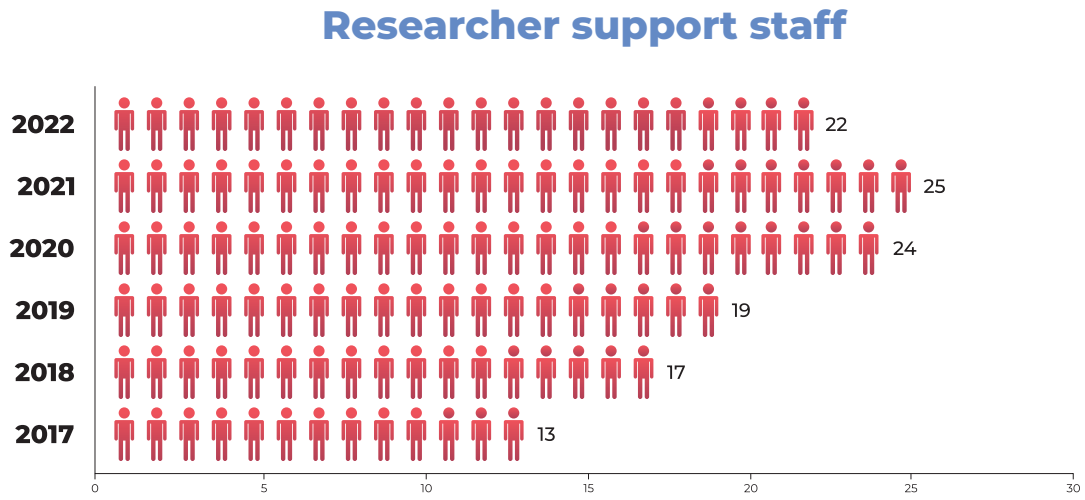


Fig. 2: Research support staff

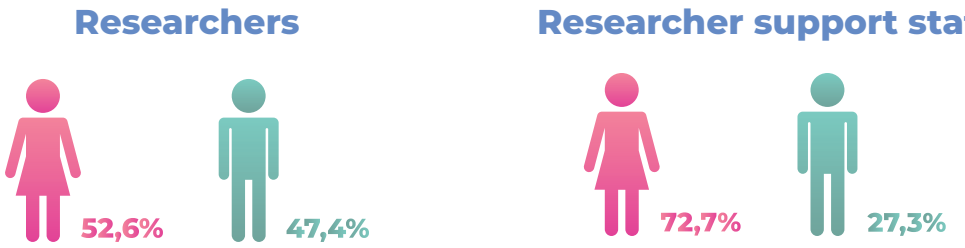


Fig. 3: Percentage breakdown by gender

More data in pills

The number of research protocols submitted to the Ethics Committee and approved has remained fairly stable, with a peak in 2020 due to the impact of COVID-19 projects (Fig. 4). Grants obtained on a competitive basis have gradually increased (Fig. 5). Details on funding sources are given in Figure 6.

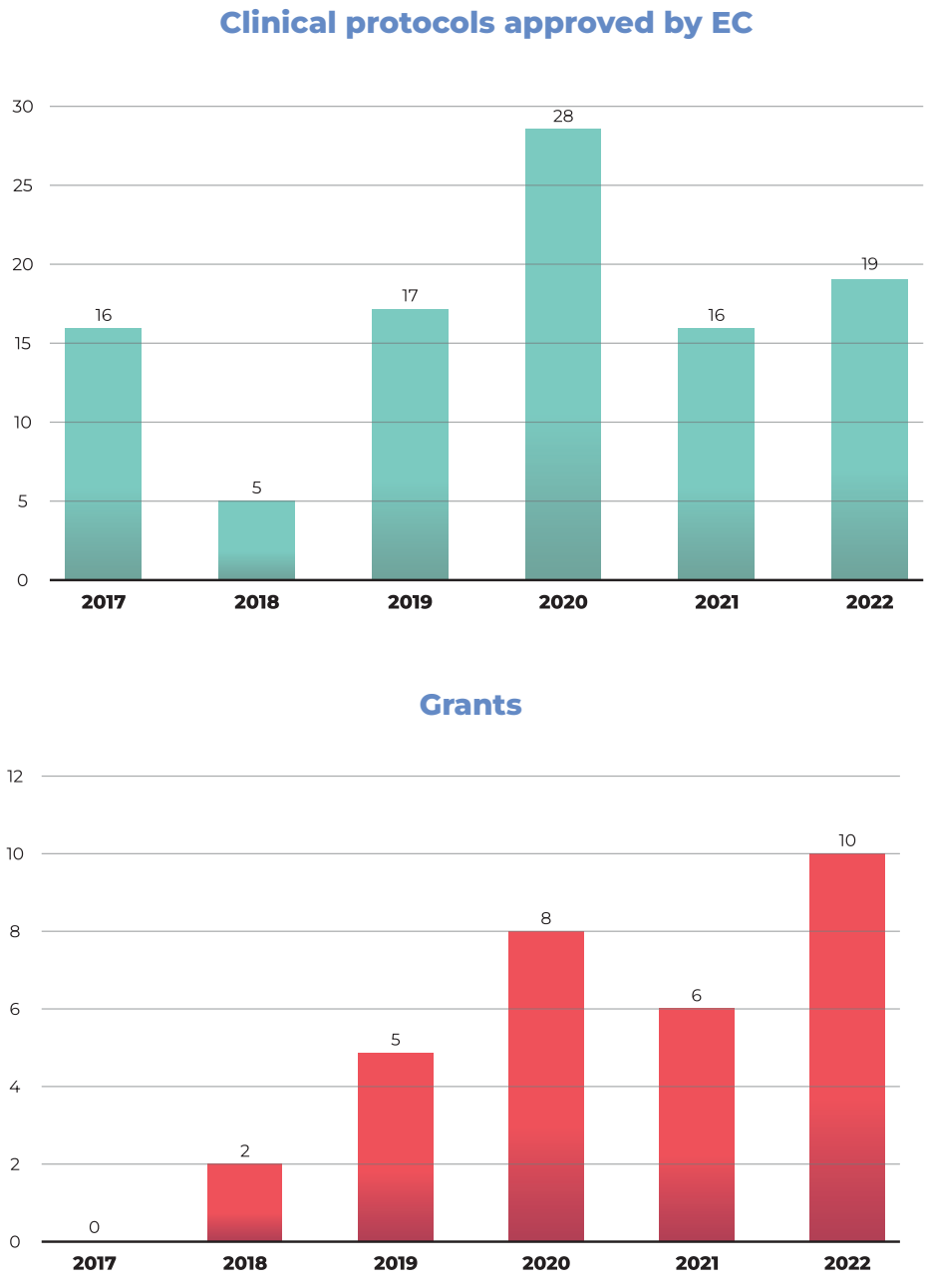


Fig. 4: research protocols submitted to the Ethics Committee and grants, 2017-2022

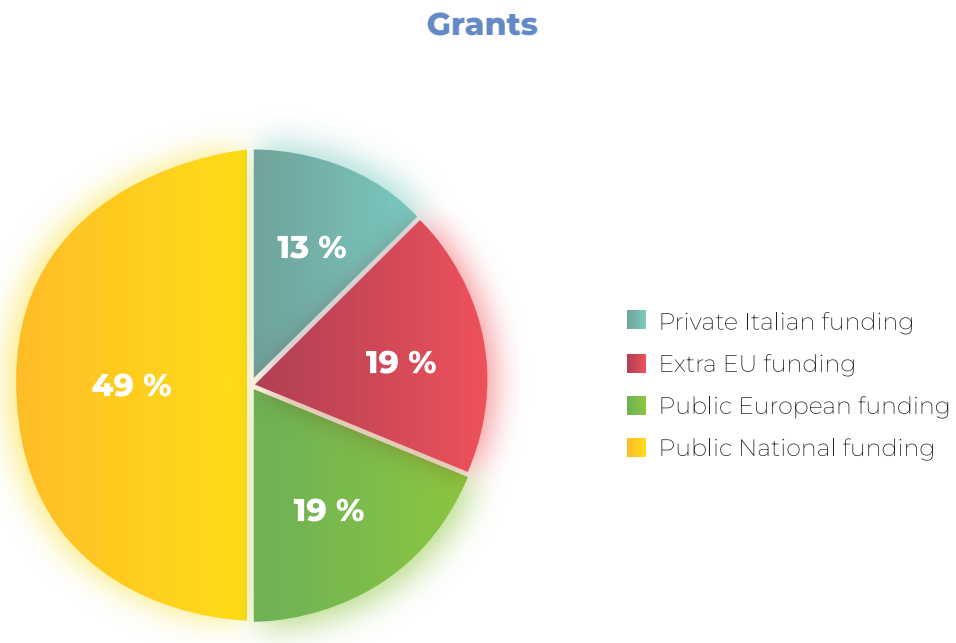


Fig. 5: percentage breakdown of grants

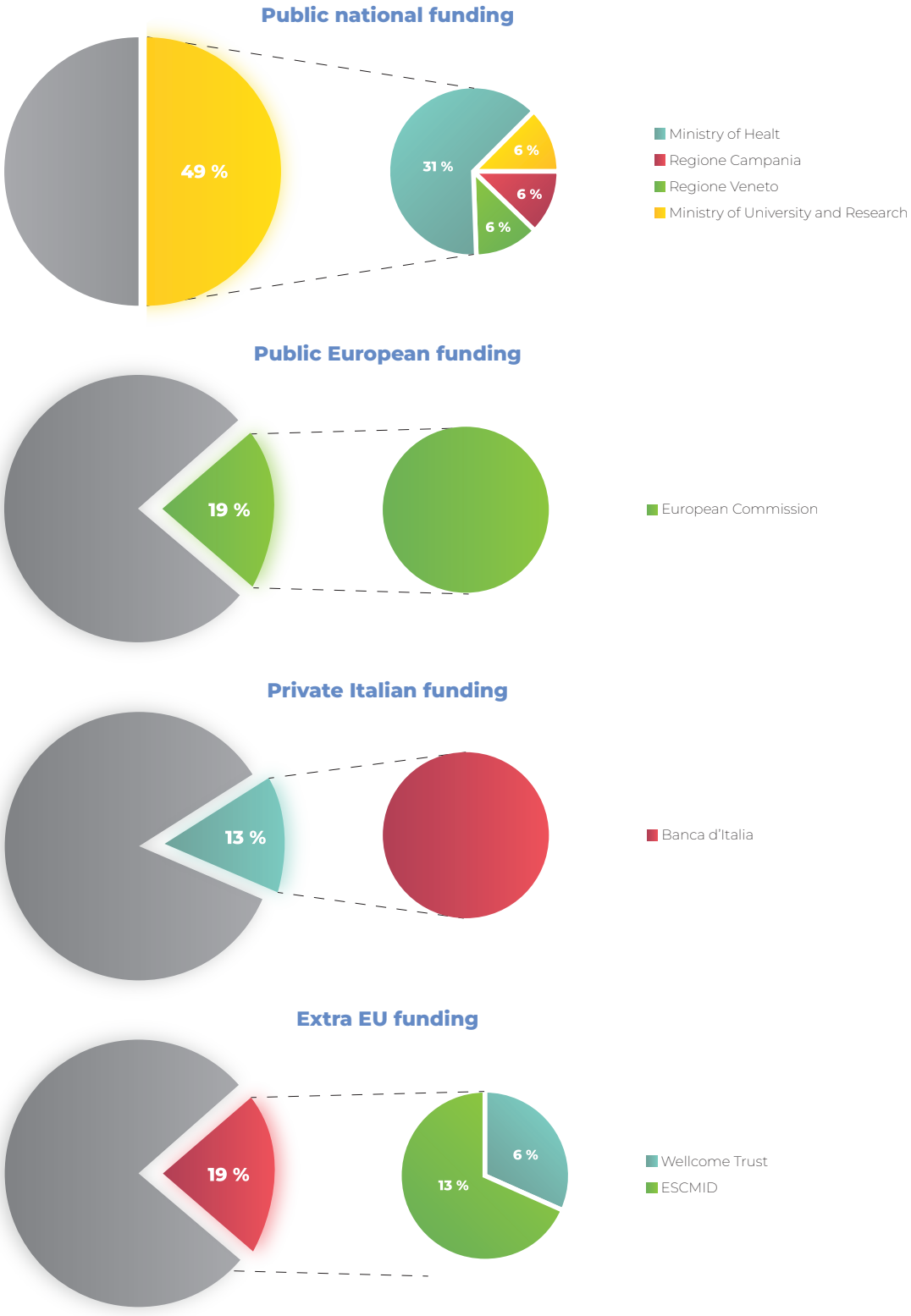


Fig. 6: percentage breakdown of grants: details

The scientific activity documented by publications and their Impact Factor has steadily increased over the years (Fig. 7).

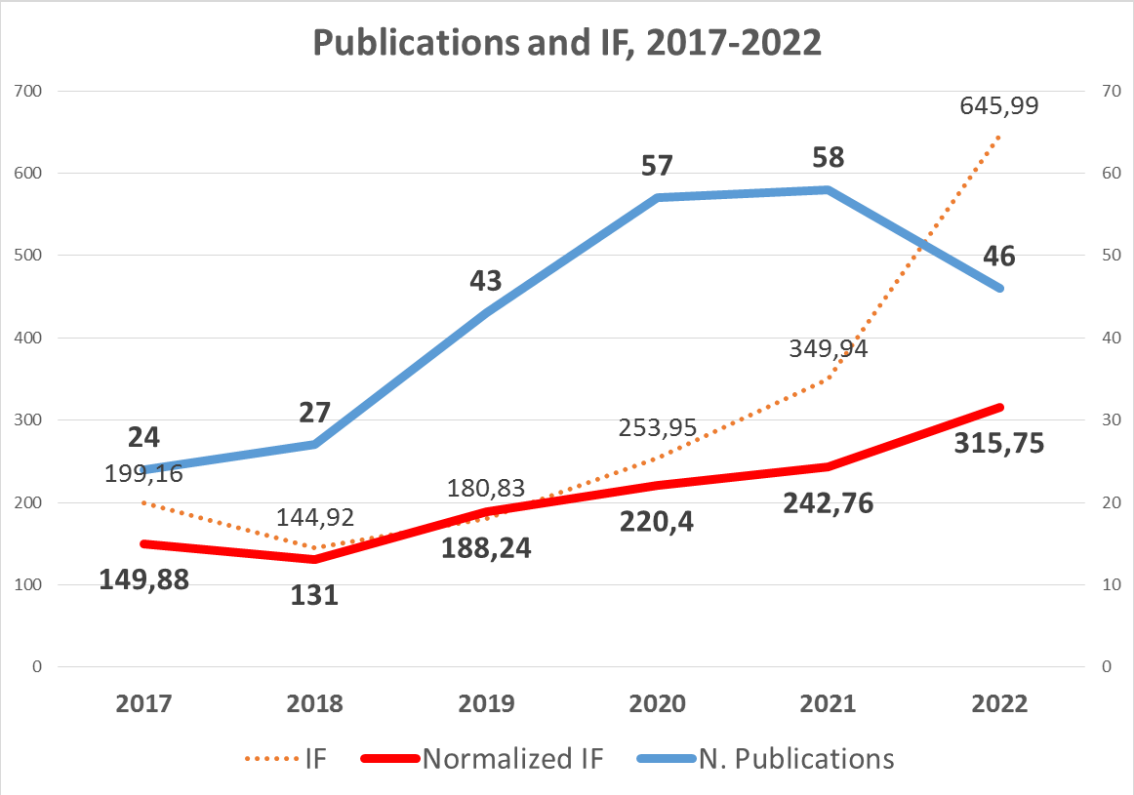


Fig. 7: Publications and Impact Factor, 2017-2022

The quality of publications is summarised by the high percentage of articles published in first quartile (Q1) and first decile (D1) journals according to Journal Citation Reports™ (Clarivate).

2020: (57 articles) Q1 31 (54,4%), D1 21 (36,8%)

2021: (58 articles) Q1 33 (56,9%), D1 19 (32,8%)

2022: (46 articles) Q1 30 (65,2%), D1 20 (43,5%)

Average productivity per researcher (Full Time Equivalent, FTE)

Year	Researchers (n.)	FTE (n.)	Normalized IF	Norm.IF/FTE
2020	37	15,95	220,40	13,82
2021	34	17	242,76	14,28
2022	38	18,65	315,75	16,93

Activity Report 2020 - 2022

Research line n. 1: Global Health: Communicable and mobility-related diseases

Line description

The objective of the research line n.1 is to study emerging infectious diseases in a global health context. COVID-19 pandemics and the recent Monkeypox outbreak are two examples of emerging infections related to the augmented global human mobility. In addition, the climate changes can influence the diffusion of vectors (e.g. arthropods) carrying pathogens that can spread human infectious diseases also outside the current endemic regions (for instance, dengue, zika, chikungunya, West Nile, malaria, etc.). For these reasons, the improvement of the surveillance capacity and preparedness against communicable and mobility-related diseases is fundamental for the near future. The purposes of this research line are: i) to acquire epidemiological and clinical data on emerging and mobility-linked infectious diseases, ii) to improve the available diagnostic and prognostic tools, ii) to expand the pathophysiology knowledge and iii) to study the host immunological response, also in relation to vaccine effect for these communicable diseases. From this perspective, our centre is involved in national one health translational Research networks (e.g. INFACT, coordinated by UniPv) and in international travel medicine, tropical medicine and global health networks (e.g. GEOSENTINEL, coordinated by the US Centers for Disease Control and Prevention, CDC and the EU TropNet, coordinated by IRCCS Sacro Cuore Don Calabria Hospital).

The research line n.1 is organized in different macro-projects, covering clinical/epidemiological and biological aspects of different diseases:

Infections in a global health perspective (Reference person: Federico Gobbi).

Progresses in the diagnosis and in the pathophysiology knowledge of emerging infectious diseases related to human mobility (Reference person: Concetta Castilletti).

Evaluation of drug efficacy for Covid-19 (Reference person: Andrea Angheben).

Clinical and epidemiological characteristics of Covid-19 (Reference person: Dora Buonfrate).

Improving the diagnosis and the pathophysiology knowledge of SARS-CoV-2 (Reference person: Chiara Piubelli).

The first two macro-projects cover different emerging infections and includes the following disease areas: vector-borne diseases (including malaria), emerging viruses, viral and bacterial fevers (including non-malarial fevers in endemic areas), tuberculosis and other mycobacterial diseases. The last three macro-projects are focused on COVID-19.

A detailed description of the obtained results from the different projects related to Research Line n.1 is reported below, according to the different disease areas.

Macro-project 1: Infections in a global health perspective

a) Projects focused on the study of critical aspects of malaria management

C_React. C-reactive protein levels in febrile tropical illnesses

- Project coordinator: DITM
- P.I. Zeno Bisoffi
- Other institutions involved: Università di Firenze, Italy. University of Oxford, UK.
- Start date: 2018
- End date: 2020

Background

In low- and middle-income countries, in resource-limited settings, the implementation of diagnostic tools discriminating bacterial from nonbacterial fever is a matter of primary concern. The introduction of malaria rapid diagnostic tests highlighted the need for point-of-care tests (POCTs) supporting clinical decision-making for non-malarial febrile illnesses.

Purpose and experimental plan

The purpose of this project was (1) to review the use of host biomarker POCTs for the assessment of acute non-malarial fever in resource-constraint settings; (2) to assess, on patients admitted to two ID wards in Italy, the best C-reactive protein (CRP) cut-off to distinguish viral from bacterial infections. Other biomarkers were evaluated

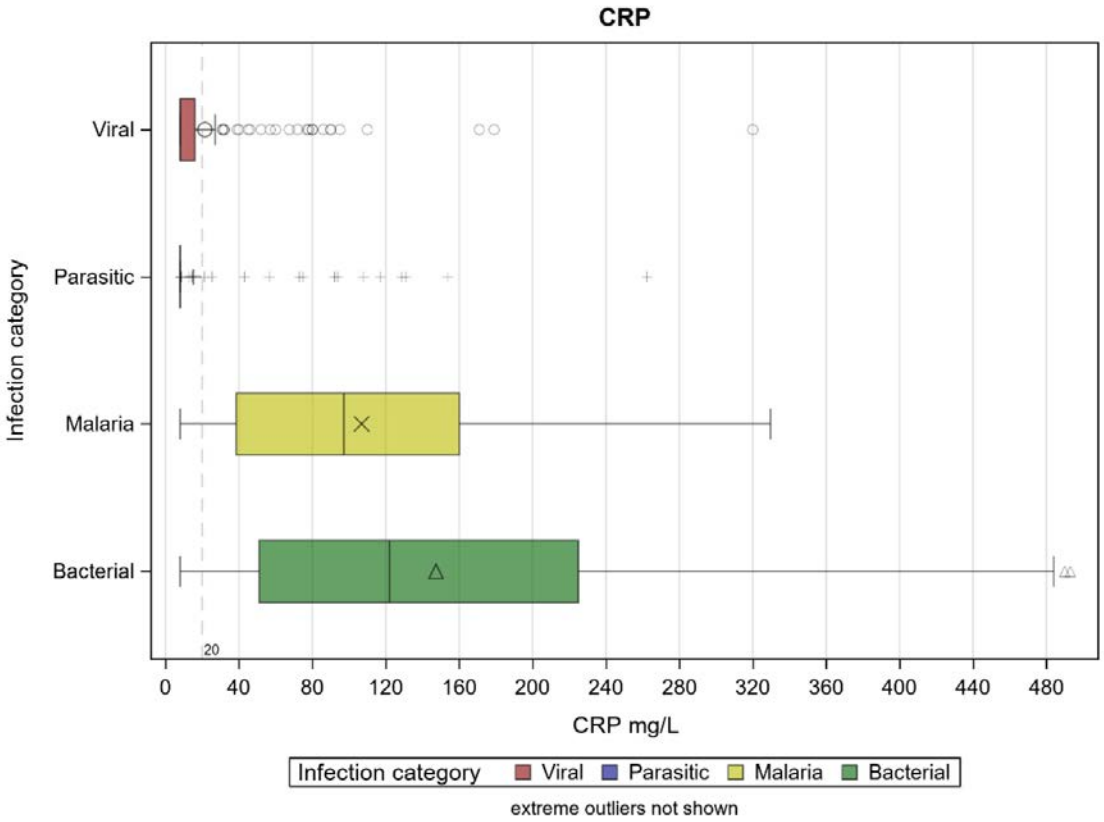
for the same purpose, alone or in combination with CRP.

For the first purpose we conducted a systematic review of the literature. For the second purpose we retrospectively analyzed the medical records of 1193 febrile cases admitted to our department and to the Department of Infectious Diseases of the University Hospital in Florence.

Results

1. CRP was the one most frequently studied and had a good accuracy to distinguish bacterial from nonbacterial infections. However, the optimal cutoff of CRP could not be assessed, and we found insufficient evidence about its impact on antibiotic prescription and clinical outcome.

1. CRP had the best accuracy in differentiating viral from bacterial infections. The best performance of CRP was a cut-off of 11 mg/L. All other biomarkers studied had significantly lower accuracy.



CRP levels according to infection category. Extreme outliers are not shown

Publications

- Bertoli G et al. Trop Med Hyg. 2020. https://doi.org/10.4269/ajtmh.19-0935
- Bertoli G et al. Diagnostics. 2021 https:// doi.org/10.3390/diagnostics11091728

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

MalAntibodies. Dynamics of anti-malarial antibodies in non-immune patients

- Project coordinator: DITM
- P.I. Zeno Bisoffi

Background and purpose

Malaria is a major travel medicine issue. Retrospective confirmation of a malaria episode diagnosed in an endemic area can have relevant implications in transfusional medicine in Europe, where blood donors are excluded from donation on the basis of positive malaria serology. However, there is scarce evidence on the dynamics of anti-malarial antibodies after a first malaria episode in non-immune individuals. The first aim of this study was to describe the dynamics of anti-malarial antibodies in a first malaria episode in non-immune travellers. Secondary objectives were to assess the sensitivity of serology for a retrospective diagnosis in non-immune travellers diagnosed while abroad and to discuss the implications in transfusional medicine.

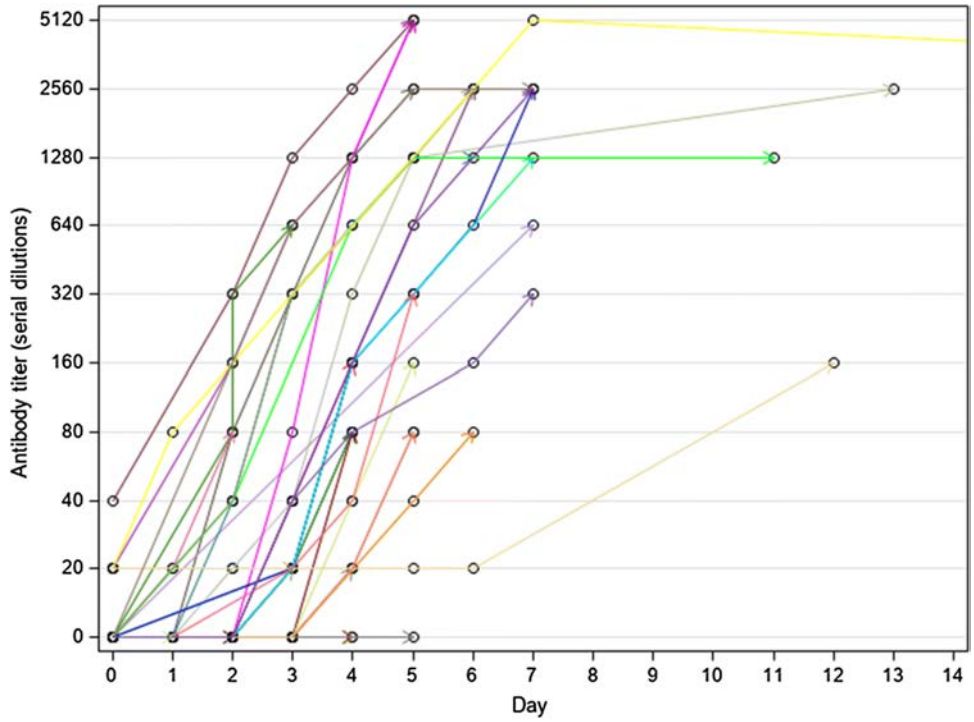
Methods

Retrospective analysis of the results of an indirect fluorescence antibody test (IFAT) for malaria available for patients with a first malaria episode by *Plasmodium falciparum* and admitted at the IRCCS Sacro Cuore Don Calabria hospital in a 14-year period. The antibody titres were collected at baseline and during further follow up visits. Epidemiological, demographic and laboratory test results (including full blood count and malaria parasite density) were anonymously recorded in a study specific electronic Case Report Form created with OpenClinica software. Statistical analysis was performed with SAS software version 9.4.

Results

Thirty-six patients were included. Thirty-four were Europeans. Median length of fe-

ver before diagnosis was 2 days (IQR 1–3). Thirty-five patients had seroconversion between day 1 and day 4 from admission, and the titre showed a sharply rising titre, often to a very high level in a few days. Only a single patient remained negative in the first 5 days from admission, after which he was no more tested. Six patients were followed up for at least 2 months, and they all showed a decline in IFAT titre, tending to seroreversion (confirmed in one patient with the longest follow up, almost 4 years). Serology demonstrated reliable for retrospective diagnosis in non-immune travellers. The decline in the anti-malarial titre might be included in the screening algorithms of blood donors, but further studies are needed.



Evolution of antibody titre during hospitalization (all 36 patients, including one who was still in hospital after 2 weeks). Dots represent the time a sample was tested. Last tested sample is represented by an arrow and coincides with the last day of hospitalization

Publications

- Bisoffi, Z., et al. Malar J, 2020. https://doi.org/10.1186/s12936-020-03300-x

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

HaemoArt. Haemolysis following oral artemisinin treatment

- Project coordinator: Florian Kurt, Charité Berlin
- DITM P.I Federico Gobbi
- Other institutions involved: University of Cologne, Cologne, Germany. Robert Koch-Institut, Berlin, Germany.
- Start date: 2018
- End date: 2022

Background and purpose

Artemisinin combination therapy (ACT) for the treatment of malaria is highly effective, well tolerated and safe. Episodes of delayed hemolysis occur in up to 57.9% of patients with severe malaria treated with intravenous artesunate, mainly caused by 'pitting' of infected red blood cells (RBCs) in the spleen and delayed loss of these once-infected RBCs (oiRBCs). Several reports indicate that post-treatment hemolysis (PTH) also occurs in uncomplicated malaria treated with oral ACT, calling for systematic investigation.

Methods

Prospective observational study to identify the proportion of patients with PTH after oral ACT, defined as increased lactate dehydrogenase activity and low haptoglobin level on day 14 after treatment. Patients were enrolled at two study centres in Germany and Italy. Study visits took place on days 1, 3, 7, 14, 28. Laboratory investigations included extended clinical routine laboratory tests, quantitative P.f.-HRP2, anti-RBC antibodies, and oiRBCs. State of semi-immunity to malaria was assessed from childhood and ongoing exposure to Plasmodium spp. as per patient history.

Results

A total of 134 patients were recruited. Thirty-seven (37.4%) of 99 with P.f. and none of nine with non-P.f. malaria exhibited PTH on d14. Patients with PTH had higher parasitaemia, higher once-infected RBCs (oiRBC) counts on d3, and a 10-fold decrease in oiRBCs between d7 and d14 compared to patients without PTH. In pat ients with PTH, loss of haemoglobin (Hb) was 4-fold greater in non-Africans than in Africans. Semi-immune African patients with PTH showed markedly increased erythropoiesis on d14 compared to not semi-immune African and non-African patients. PTH is

common in patients with uncomplicated malaria and oral ACT. While the loss of Hb will not be clinically relevant in most cases, it could aggravate pre-existing anaemia.

Publications

- Kurth F: et al. Submitted end 2022 to Journal of Trav. Med.

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

SafeArt. Safety registry for malaria patients treated with artenimol-piperaquine

- Project coordinator: Ron Behrens, for TropNet
- DITM P.I Zeno Bisoffi
- Other institutions involved: TropNet affiliated institutions.
- Start date: 2019
- End date: 2021

Background and purpose

European travellers to endemic countries are at risk of malaria and may be affected by a different range of co-morbidities than natives of endemic regions. The safety profile, especially cardiac issues, of artenimol (previously dihydroartemisinin)-piperaquine (APQ) Eurartesim® during treatment of uncomplicated imported falciparum malaria is not adequately described due to the lack of longitudinal studies in this population. The present study was conducted to partially fill this gap.

Methods

Participants were recruited through Health Care Provider's safety registry in 15 centres across 6 European countries in the period 2013-2016. Adverse events (AE) were collected, with a special focus on cardiovascular safety by including electrocardiogram QT intervals evaluated after correction with either Bazett's (QTcB) or Fridericia's (QTcF) methods, at baseline and after treatment. QTcB and/or QTcF prolongation were defined by a value > 450 ms for males and children and > 470 ms for females.

Results

75 patients reported a total of 129 AE (27 serious), 46 being suspected to be related to APQ (11 serious). Women and Non-African participants had significantly ($p < 0.05$) more AEs. Among AEs, 21 were due to cardiotoxicity (7.1%), mostly QT prolongation, while 6 were due to neurotoxicity (2.0%), mostly dizziness. QT prolongation was observed in 17/143 participants (11.9%), 2 of them reporting > 500 ms (milliseconds) but with no clinical symptoms. A trend towards increased prolongation was observed in those over 65 years of age. No new safety signal was reported. The overall efficacy rate was 255/257 (99.2%). APQ appears as an effective and well-tolerated drug for treatment of malaria in patients recruited in European countries.

Publications

- Vignier et al, Malaria J, 2021. https://doi.org/10.1186/s12936-021-03750-x

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

MalariaOutTreat. Outpatient treatment of imported uncomplicated Plasmodium falciparum malaria

- Project coordinator: Thomas Zoller, Charité Berlin, for TropNet
- DITM P.I Federico Gobbi
- Other institutions involved: Several institutions belonging to TropNet and GeoSentinel.
- Start date: 2018
- End date: 2020

Background and purpose

Plasmodium falciparum malaria (P.f. malaria) is frequently imported to non-endemic countries. Recommendations on outpatient treatment differ largely due to differences in country-level guidelines and even between tropical medicine referral centres within the same country.

Methods

This survey among experts from TropNet or GeoSentinel referral centres for tropical medicine outside malaria endemic areas investigated common practices in P.f. malaria management, selection criteria for outpatient management and diagnostic procedures as a first step for developing a future common and evidence-based approach.

Results

The threshold parasitaemia for outpatient treatment varied from 0.1 to 5% with a median of 2%. A median of 0.5% of outpatients were admitted during follow-up. During the last 10 years, 33 complications were reported by nine of the 27 centres and three deaths by one centre.

Publications

- Lingscheid T. et al, Journal trav. Med., 2021. https://doi.org/10.1093/jtm/taaa082

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

b) Projects focused on other vector-borne infections and other mobility related diseases.

Scrub tyhp. Outbreak of imported scrub typhus and literature review

- Project coordinator: DITM
- P.I. Federico Gobbi
- Start date: 2020
- End date: 2021

Background and purpose

Scrub typhus is a vector-borne rickettsial infection, which can cause relevant morbidity and mortality. While the number of cases is around a million per year globally, the infection is seldom diagnosed in travellers from Europe.

Methods

Case report of three cases diagnosed in Italian travellers. Review of the literature about imported cases in Europe in the last 60 years.

Results

Three participants to the same hiking trip to the forest of northern Laos presented fever and other symptoms, including eschars (2 individuals) and skin rash (2 individuals). Overall, they didn›t report complications, and recovered soon after doxycycline treatment. Diagnosis was retrospectively confirmed with PCR in one of them. The review collected data from 40 patients. Almost all of them (95%) presented fever, more than a half had headache, skin rash, eschars, arthromyalgias. 73% of them were hospitalized, and 16.2% needed intensive care. Diagnosis was confirmed by serology in almost all cases (94.6%). Most patients (88%) were treated with doxycycline. All patients survived, although one case resulted in incomplete tetraparesis.

Publications

- Costa C. et al. Trav Med and Inf Dis, 2021. https://doi.org/10.1016/j.tmaid.2021.102062

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

Dengue_Ita. First autochthonous dengue cluster in Italy.

- Project coordinator: DITM
- P.I. Federico Gobbi
- Other institutions involved: University of Padova, Italy. San Bortolo Hospital, Vicenza, Italy. AULSS 8, Vicenza, Italy. Istituto Zooprofilattico Sperimentale delle Venezie, Legnaro, Padova, Italy. Regione Veneto, Venice, Italy.
- Start date: 2020
- End date: 2021

Background and purpose

In August 2020, during the coronavirus disease (COVID-19) pandemic, five locally acquired cases of dengue virus type 1 were detected in a family cluster in Vicen-

za Province, North-East Italy where *Aedes albopictus* mosquitoes are endemic. The primary case was identified in a young woman, who developed fever after returning from Indonesia to northern Italy, on 27 July 2020. She spent the mandatory quarantine for COVID-19 at home with relatives, six of whom developed dengue within two weeks. This is the first outbreak of autochthonous dengue reported in Italy.

Methods

Clinical description of the cluster and epidemiological/entomological investigation according to the national and regional arbovirus surveillance plan. Dengue cases were followed-up with weekly visits and laboratory tests until recovery and clearance of viral RNA from blood.

Results

Epidemiological investigation identified further five autochthonous dengue cases. The last case of the outbreak developed fever on 29 September 2020. DENV-1 RNA was detected in blood and/or urine in all autochthonous cases, up to 35 days after fever onset. All cases developed IgM and IgG antibodies which cross-reacted with West Nile virus (WNV) and other flaviviruses. Sequencing of the full viral genome showed over 99% nucleotide identity with DENV-1 strains isolated in China in 2014-2015; phylogenetic analysis classified the virus within Genotype I. Entomological site inspection identified a high density of *Aedes albopictus mosquitoes*.

Clinical, epidemiological and laboratory parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Date of symptom onset	30 Jul	16 Aug	16 Aug	16 Aug	18 Aug	18 Aug
Delay between sample collection and onset of symptoms (days)	27	10	6	10	8	8
Symptoms	Fever (38° C), arthralgia, myalgia, headache	Fever (39° C), arthralgia, myalgia, headache	Fever (38° C), arthralgia, upper limb itching	Fever (38° C)	Fever (38.5° C)	Fever (39° C)
Epidemiological link	Source case	Household contact of Case 1	Index case and household contact of Case 1	Household contact of Case 1	Household contact of Case 1	Household contact of Case 1
DENV RNA in blood[a]	Negative	DENV-1	DENV-1	Negative	DENV-1	DENV-1
DENV RNA in urine[a]	Negative	DENV-1	DENV-1	DENV-1	DENV-1	DENV-1
DENV RNA in saliva[a]	Negative	Negative	DENV-1	Negative	DENV-1	DENV-1
DENV NS1 antigen[b]	Negative	Positive	Positive	Negative	Positive	Positive
DENV IgM[c]	Positive	Positive	Negative	Positive	Positive	Positive
DENV IgG[c]	Positive	Negative	Negative	Negative	Negative	Negative

RT: reverse transcriptase; US: United States.

[a] For DENV RNA testing, total nucleic acids were purified from 200 µL of plasma, urine and saliva by using a MagNA Pure 96 System (Roche Applied Sciences, Basel, Switzerland). DENV RNA was amplified by in-house, real-time RT-PCR methods, which allowed discrimination between the different serotypes, according to the Center for Disease Control and Prevention protocol [13]. Real-time RT-PCR assays were carried out using the one-step, real-time kit (Thermo Fisher Scientific, Waltham, Massachusetts, US) and run on ABI 7900HT Sequence Detection Systems (Thermo Fisher Scientific).

[b] DENV NS1 antigen was detected in plasma by using a rapid immunochromatographic assay (dengue NS1 Ag Strips, Bio-Rad, Hercules, California, US).

[c] DENV IgM and IgG antibodies were detected by a chemiluminescence immunoassay (VirClia, Vircell, Granada, Spain) in a Thunderbolt instrument (Vircell).

Clinical and laboratory findings in outbreak (family cluster) of autochthonous dengue, Vicenza Province, Italy, July to August 2020 (n=6)

Publications

- Lazzarini L. et al, Eurosurv, 2020. https://doi.org/10.2807/1560-7917 ES.2020.25.36.2001606
- Barzon L. et al, Journal of Travel Medicine, 2021. https://doi.org/10.1093/jtm/taab130

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

Arbo-Score. A Rapid Score for Early Identification of Patients with Imported Arbovirosis Caused by Dengue, Chikungunya and Zika Virus

- Project coordinator: Università di Firenze, Italy.
- DITM P.I. Federico Gobbi.
- Start date: 2020
- End date: ongoing

Background and purpose

Chikungunya (CHIKV), Dengue (DENV), and Zika (ZIKV) viruses present significant clinical and epidemiological overlap, making an accurate and rapid diagnosis challenging. Timely activation of preventive vector control measures is crucial to avoid outbreaks in non-endemic settings. Diagnosis is based on combination of serological and molecular assays which could be time consuming and sometimes disappointing.

Methods

Retrospective case-control study carried out at a tertiary teaching hospital in Italy, including all febrile subjects returning from tropical countries during the period 2014-2019. Controls were travelers with other febrile illnesses who tested negative in laboratory analysis for CHIKV, DENV, ZIKV arbovirosis. A score weighted on the regression coefficients for the independent predictors was generated.

Results

Ninety patients were identified: 34 cases (22 DENV, 4 CHIKV, and 8 ZIKV) and 56 controls. According to our results, myalgia, cutaneous rash, absence of respiratory symptoms, leukopenia, and hypertransaminasemia showed the strongest association with arbovirosis. Combining these variables, we generated a scoring model that showed an excellent performance (AUC 0.93). A handy and simple score, based on three clinical data (myalgia, cutaneous rash and absence of respiratory symptoms) and two laboratory results (leukopenia and hypertransaminasemia), provides a useful tool to help diagnose arboviral infections and appropriately activate vector control measures in order to avoid local transmission.

Publications

Vellere I. et al, microorganisms, 2020. https://doi.org/10.3390/microorganisms8111731

Funding

Ministry of Education, University and Research (Italy) Excellence Departments 2018–2022 Project for the Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy.

MolARBO. Molecular techniques for the detection of West Nile, Dengue, Zika and Chikungunya arboviruses: a narrative review

- Project coordinator: DITM
- P.I. Antonio Mori
- Start date: 2020
- End date: 2021

Background and purpose

Molecular technology has played an important role in arboviruses diagnostics. PCR-based methods stand out in terms of sensitivity, specificity, cost, robustness, and accessibility, and especially the isothermal amplification (IA) method is ideal for field-adaptable diagnostics in resource-limited settings (RLS). In this review, we provide an overview of the various molecular methods for West Nile, Zika, Dengue and Chikungunya.

Methods

We summarize literature works reporting the assessment and use of in house and commercial assays. We describe limitations and challenges in the usage of methods and opportunities for novel approaches such as NNext-GenerationSequencing (NGS).

Results

The rapidity and accuracy of differential diagnosis is essential for a successful clinical management, particularly in co-circulation area of arboviruses. Several commercial diagnostic molecular assays are available, but many are not affordable by RLS and not usable as Point-of-care/Point-of-need (POC/PON) such as Real-TimeRT-PCR, Array-based methods and NGS. In contrast, the IA-based system fits better for POC/PON but it is still not ideal for the multiplexing detection system. Improvement in the characterization and validation of current molecular assays is needed to optimize their translation to the point of care.

Publications

Mori A., et al, Exp Rev of Molec Diagnostics, 2021. https://doi.org/10.1080/14737159.2021.1924059

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

HIV_YellowVac. Immunogenicity and Duration of Protection After Yellow Fever Vaccine in People Living with HIV: A Systematic Review.

- Project coordinator: Université Libre de Bruxelles, Brussels, Belgium.
- DITM P.I. Dora Buonfrate.
- Other institutions involved: Robert Koch Institute, Berlin, Germany.

Background and purpose

We lack the rationale on which to base the development of a yellow fever (YF) vaccination schedule for people living with human immunodeficiency virus (PLWHIV). Aim of the study was to report on the current evidence regarding the seroconversion

rate and the duration of humoral protection after YF vaccine, as well as the impact of revaccination in PLWHIV.

Methods

MEDLINE, Google Scholar, LILACS and Cochrane CENTRAL were searched. We selected studies on PLWHIV of all ages (including perinatally HIV-infected patients) and all settings (YF endemic and non-endemic zones). Intervention investigated was vaccination against YF, at least once after the HIV diagnosis. The research questions were the seroconversion rate, duration of humoral immunity after YF vaccine and impact of revaccination in PLWHIV. Selected studies were assessed for quality using the Newcastle-Ottawa scale.

Results

Ten, six and six studies were selected for the systematic review of each question, respectively. Only one study addressed the first question in perinatally HIV-infected children. The quality of the studies was assessed as Poor (n = 16), Fair (n = 2) or Good (n = 4). A meta-analysis demonstrated that 97.6% (95% CI 91.6%-100%) of the included population seroconverted. Between 1 and 10 years after YF vaccine, reported persistence of neutralizing antibodies was 72% (95% CI 53.6%-91%), and it was 62% (95% CI 45.4%-78.6%) more than 10 years after YF vaccine. No conclusions could be drawn on impact of revaccination because of the small number of patients.

Publications

Martin C. et al, Clinical Microbiology and Infection, 2021. https://doi.org/10.1016/j.cmi.2021.03.004

Funding

None

EURaDMoG. European expert network on rare communicable diseases and other rare diseases linked to mobility and globalisation focused on health care provision: a feasibility study

- Project coordinator: ISGlobal Barcelona, Spain
- DITM P.I.: Dora Buonfrate
- Other institutions involved: TropNet and EuroTravNet affiliated institutions.

Background and purpose

In the current mobility and globalization context, there is a growing need to identify potential changes on the pattern of diseases in the European Union (EU)/European Economic Area (EEA) and provide accurate diagnosis and treatment for the population. The pattern of rare communicable diseases that can affect people returning to EU/EEA from travel abroad, visiting EU/EEA or establishing in the EU/EEA is of special relevance. The objective of this manuscript is to give an overview about the EURaDMoG study and discuss the feasibility of establishing a European network on rare communicable diseases and other rare conditions linked to mobility and globalization.

Methods

We undertook a three-steps process where we first conducted a narrative review to estimate the prevalence and incidence and to list rare communicable and non-communicable diseases linked to mobility and globalization in the EU/EEA; second, we organized an international consultation workshop with experts in the diseases previously selected; and finally, the feasibility study analysed how successful a European expert network on rare diseases linked to mobility and globalization focused on health care provision would be, accounting for different operational and also sustainability criteria.

Results

Three scenarios were considered: 1) To maintain the current situation “Status Quo” scenario; 2) to create a specific European expert network (EEN) on rare communicable diseases linked to mobility and globalisation; 3) to develop a new ERN on communicable rare diseases linked to mobility and globalisation. Since the focus is the provision of health care, an ERN could have the potential to better boost the quality of care being facilitated by technological tools and online platforms that permit the safe and ethically acceptable exchange of data. However, this potential new network

should not eclipse current existing networks and they should be complementary.

Publications

Requena-Méndez A. et al, OJRD, 2020. https://doi.org/10.1186/s13023-020-01534-1

TravInf. Travel-related infections presenting in Europe: A 20-year analysis of EuroTravNet surveillance data

- Project coordinator: GeoSentinel-EuroTravNet
- DITM P.I.: Federico Gobbi
- Other institutions involved: GeoSentinel-EuroTravNet affiliated institutions.

Background and purpose

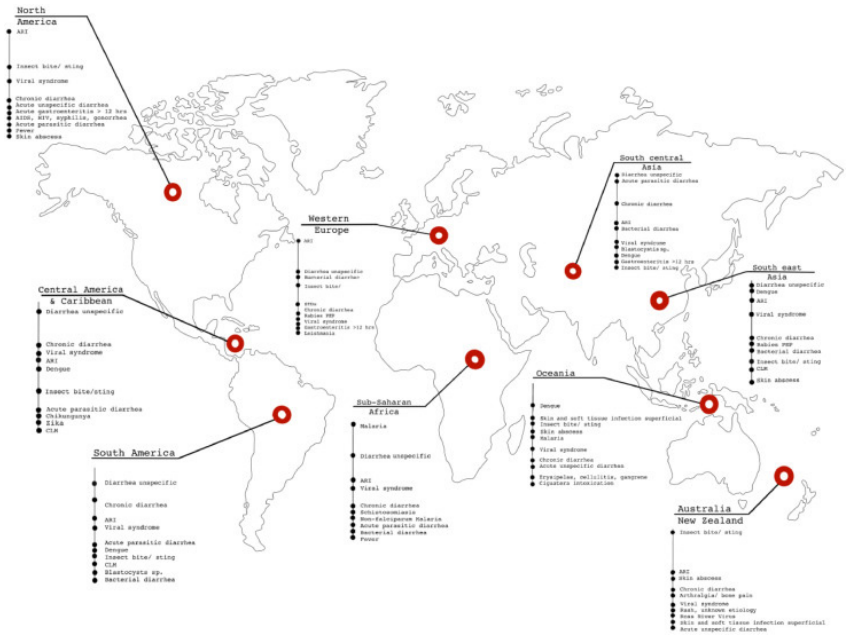
Disease epidemiology of (re-)emerging infectious diseases is changing rapidly, rendering surveillance of travel-associated illness important.

Methods

We evaluated travel-related illness encountered at EuroTravNet clinics, the European surveillance sub-network of GeoSentinel, between March 1, 1998 and March 31, 2018.

Results

103,739 ill travellers were evaluated, including 11,239 (10.8%) migrants, 89,620 (86.4%) patients seen post-travel, and 2,880 (2.8%) during and after travel. In 5-year increments, greater proportions of patients were migrants or visiting friends and relatives (VFR). Falciparum malaria was amongst the most-frequently diagnosed illnesses with 5,254 cases (5.1% of all patients) and the most-frequent cause of death (risk ratio versus all other illnesses 2.5:1). Animal exposures requiring rabies post-exposure prophylaxis increased from 0.7% (1998-2002) to 3.6% (2013-2018). There were 44 cases of viral haemorrhagic fever. Arboviral infection numbers increased significantly.



Top 10 diagnoses by region of acquisition in travelers seen after travel

Publications

Grobush MP et al, Lancet Reg. Health-Europe, 2021. https://doi.org/10.1016/j.lanepe.2020.100001

Buonfrate D. et al, Lancet Reg. Health-Europe, 2021 https://doi.org/10.1016/j.lanepe.2020.100006

Toxolta. Epidemiological distribution and clinical correlates of T. gondii strains in Italians and foreigners visited in two referral centers in Northern Italy.

- Project coordinator: DITM
- P.I. Sara Caldrer
- Other institutions involved: IRCCS San Matteo Hospital, Pavia and University of Pavia, Italy.
- Start date: 2020
- End date: 2022

Background and purpose

Toxoplasma gondii is a protozoan parasite responsible for human toxoplasmosis. The three major clonal lineages and different recombinant strains of T. gondii have a varied global distribution. This study aimed at evaluating the epidemiological distribution of types II and I-III and recombinant or mixed T. gondii in Italians and foreigners residing in Italy, establishing an association between serotypes and demographic characteristics. Serotype II of T. gondii was the most prevalent in the Italian population, whereas type I-III was the most prevalent in the foreign group. Surprisingly, we observed a notable amount of recombinant or mixed serotypes in European and Italian subjects. Moreover, we showed a significant difference in the prevalence of T. gondii serotypes between men and women, Italians, and foreigners. This descriptive study is the first to investigate the epidemiological distribution of T. gondii serotypes in humans in Italy using a homemade ELISA. We considered this technique suitable for discriminating between serotypes II and I-III and, consequently, for an epidemiological study focusing on the observation of circulating T. gondii strains and clinical correlations.

Methods

We collected the sera of 188 subjects who had tested positive for specific T. gondii antibodies. The population was differentiated into groups based on sex, nationality, and place of birth (Italy, Africa, South America, Asia, or Europe (except Italy)). We then performed a homemade ELISA test that detected both the antibodies against the amino acid sequences of the three main genotype antigens (I-III) in human sera and discerned the T. gondii strains.

Results

Serotype II of T. gondii was the most prevalent in the Italian population, whereas type I-III was the most prevalent in the foreign group. Surprisingly, we observed a notable amount of recombinant or mixed serotypes in European and Italian subjects. Moreover, we showed a significant difference in the prevalence of T. gondii serotypes between men and women, Italians, and foreigners. This study is the first to investigate the epidemiological distribution of T. gondii serotypes in humans in Italy using a homemade ELISA. We considered this technique suitable for discriminating between serotypes II and I-III and, consequently, for an epidemiological study focusing on the observation of circulating T. gondii strains and clinical correlations.

Publications

Caldrer S, Vola A, Ferrari G, Ursini T, Mazzi C, Meroni V, Beltrame A. Toxoplasma gondii Serotypes in Italian and Foreign Populations: A Cross-Sectional Study Using a Home-

made ELISA Test. Microorganisms. 2022 Aug 5;10(8):1577. https://doi.org/10.3390/microorganisms10081577 PMID: 36013995; PMCID: PMC9415598

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

LymeVerona. Emergence of Lyme borreliosis in the province of Verona, Northern Italy: Five-years of sentinel surveillance

- Project coordinator: DITM
- P.I.: Anna Beltrame
- Other institutions involved: Directorate of Prevention, Veneto Region, Italy

Background and purpose

Since 2006, 1259 total LB cases have been reported in the Veneto region. In the Verona province, a maximum of two cases had been reported each year up to 2015, while since 2016, there has been a substantial and progressive increase: 12 cases in 2016, 13 cases in 2017, 41 cases in 2018, and 31 cases in 2019. The aim of this study is to describe the LB cases diagnosed in a single hospital located in the province of Verona (Veneto region), Italy, over a five-year period, with particular emphasis on the incidence time trend of LB and geographical location of risk exposure, demographic and epidemiological characteristics, clinical manifestations, laboratory data, and treatment of affected patients.

Methods

We investigated the epidemiology, clinical manifestations, laboratory data and antibiotic treatment of Lyme borreliosis in the province of Verona, Northern Italy, during the period 2015-2019.

Results

One hundred and 29 cases of Lyme borreliosis were diagnosed in a single hospital representing 27 % of all cases reported in the Veneto region in the same period. Early localized Lyme borreliosis was the most common presentation (74 %), followed by early disseminated Lyme borreliosis (21 %). One possible early Lyme neuroborreliosis and two cranial neuropathies were diagnosed. IgM and/or IgG borrelia antibodies were positive in 90 % of the cases. This significant increase of Lyme borreliosis in-

cidence in the province of Verona highlights the need to increase knowledge on its epidemiology and clinical manifestation among both the general population and clinicians to allow early diagnosis and treatment.

Publications

Beltrame A., et al, Ticks and Tick-borne Diseases, 2021. https://doi.org/10.1016/j.ttbdis.2020.101628

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

Macro-project 2: Progresses in the diagnosis and in the pathophysiology knowledge of emerging infectious diseases related to human mobility.

MPXVOBSLab. Human Monkeypox virus viral shedding and immunological response: an observational study.

- Project Coordinator: DITM
- P.I. Concetta Castilletti
- Start date: 2022
- End date: ongoing

Background and purpose

Mpox has emerged as the most important human OPXV infection after the eradication of smallpox. First mpox outbreak outside endemic African countries was reported in USA during 2003. In May 2022, MPXV infections spread rapidly in multiple non-endemic countries leading WHO to declare the escalating global mpox outbreak a Public Health Emergency of International Concern. There are limited data available on duration of MPXV nucleic acid detectability and infectivity of detected virus; antibodies response and evolution of cell immunophenotype along the disease are poorly investigated. The better knowledge of the immune response could provide a lab correlate for further studies on exposition, vaccine response, and immunity.

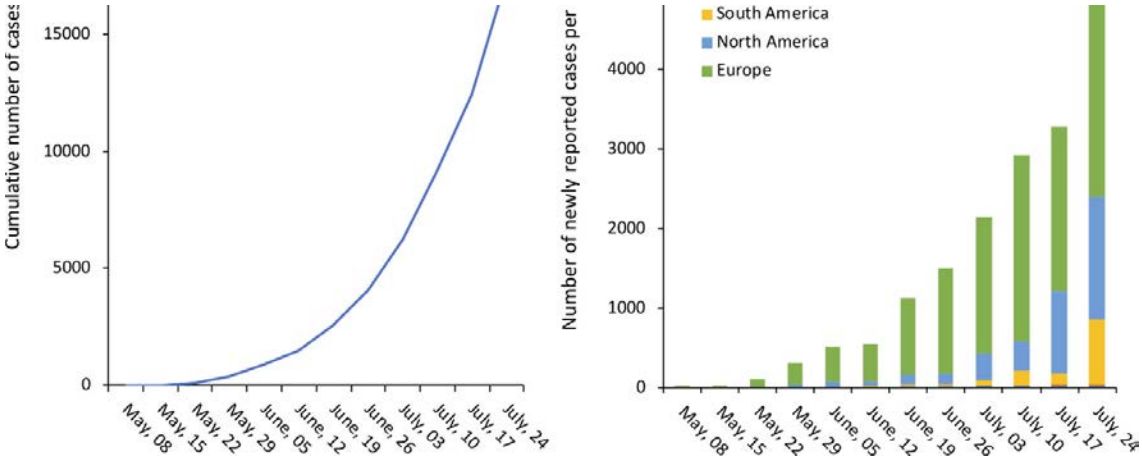
Methods

Fifteen patients with a laboratory-confirmed mpox were enrolled in this longitudinal observational cohort study. Different clinical specimens were collected at different time points after symptoms onset (SO) to perform molecular and immunological tests. In detail, a home-made immunofluorescence assay was performed to detect the presence of specific IgA, IgM and IgG. Neutralizing antibody activity and immunological memory and activation/exhaustion of T- and B-cells were also evaluated. In addition, a subgroup of nine patients was evaluated for the release of multiplex circulating cytokines involved in the inflammatory response.

Results

Serological findings demonstrated higher IgA levels early after SO compared to IgM and IgG (mean: 1:82, 1:30 and 1:29, respectively), highlighting the relevance of IgA testing in early diagnosis. Regarding the immunophenotype, most of patients developed a Th1 response. Early after SO a significant reduction of CD4+ T-cells and a parallel increase of CD8+ T-cells were observed in all patients. Notably, in HIV+ subjects lower levels in T lymphocytes and generally in CD4+ T-cells were observed. On contrary, a higher percentage of effector memory CD8+ T- cells with increase of TEMRA CD8+ T-cells over time were observed in HIV+ respect to non-HIV subjects. Our data highlight a possible different activation state of effector cells in HIV+ patients during MPXV infection.

In parallel, a literature review was drafted, and a case study on an asymptomatic infection was described (Accordini et al., submitted to Lancet Microbe, end 2022). A clinical validation of a commercial specific ddPCR test was performed (Pomari et al., paper ready for submission, end 2022). Other studies on clinical validation of different molecular tests and on the molecular characterization of MPXV genome along the epidemic are also ongoing.



Number of confirmed monkeypox cases. (A). Cumulative number of confirmed cases worldwide. (B). Number of newly reported confirmed cases per week, by continent/subcontinent. Source of original data https://www.monkeypox.global.health/, accessed on July 25, 2022

Collaborators

Division of Infectious Diseases, Department of Diagnostic and Public Health, University of Verona; and Division of Infectious Diseases, Department of Medicine, Verona University Hospital.

Publications

Capobianchi MR, et al. Front Cell Infect Microbiol. 2022. https://doi.org/10.3389/fcimb.2022.1005955

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

FalcPCR. Assessment of molecular detection of Plasmodium falciparum in whole blood and serum

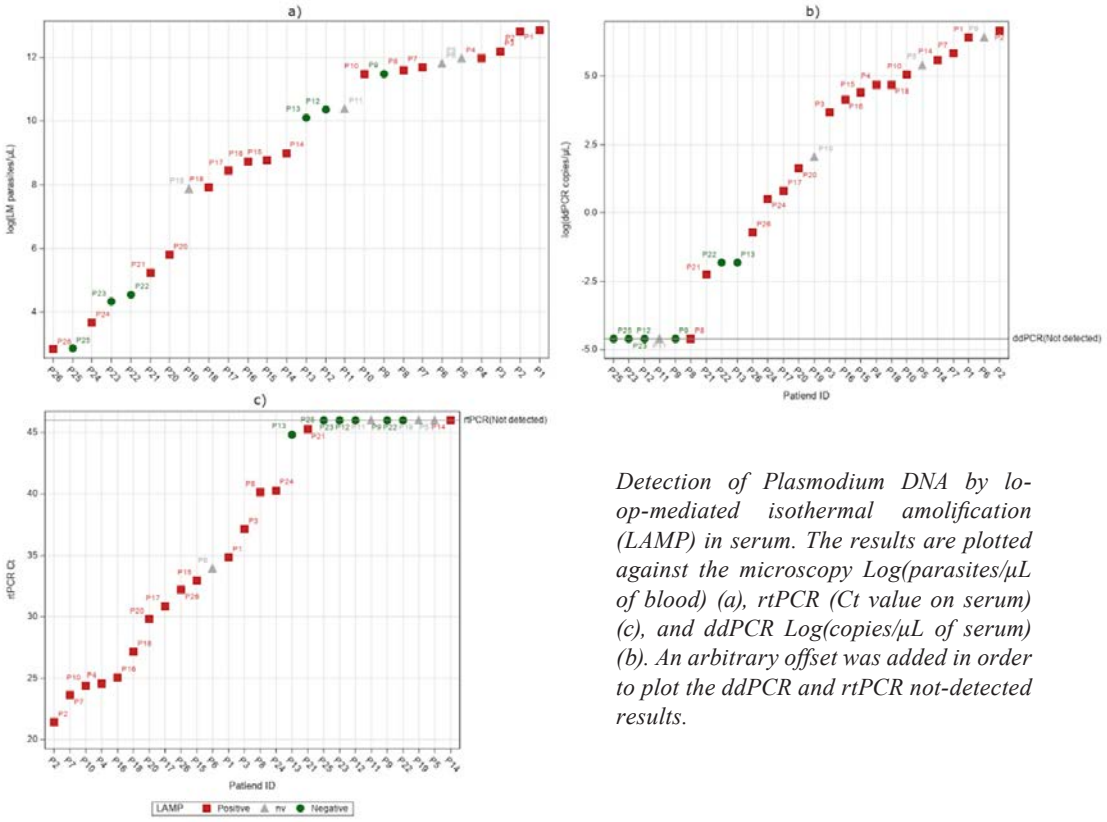
- Project coordinator: DITM
- P.I. Elena Pomari
- Start date: 2019
- End date: ongoing

Background and purpose

The estimation of *Plasmodium falciparum* parasitaemia can vary according to the method used. Recently, droplet digital PCR (ddPCR) has been proposed as a promising approach in the molecular quantitation of *Plasmodium*, but its ability to predict over, the possibility of applying the ddPCR-sensitive method to serum samples has never been explored.

Methods

We used, for the first time, ddPCR on both blood and serum to detect the DNA of *P. falciparum* in 52 paired samples from 26 patients. ddPCR was compared with loop-mediated isothermal amplification (LAMP) and rtPCR. The correlation between the ddPCR results, microscopy, and clinical parameters was examined.



Detection of Plasmodium DNA by loop-mediated isothermal amolification (LAMP) in serum. The results are plotted against the microscopy Log(parasites/µL of blood) (a), rtPCR (Ct value on serum) (c), and ddPCR Log(copies/µL of serum) (b). An arbitrary offset was added in order to plot the ddPCR and rtPCR not-detected results.

Results

In serum samples, ddPCR revealed the best performance in detecting *P. falciparum* DNA, with 77% positive samples among malaria subjects. Conclusion: Absolute quantitation by ddPCR can be a flexible technique for *Plasmodium* detection, with potential application in the diagnosis of malaria. In particular, ddPCR is a powerful ap-

proach for *Plasmodium* DNA analysis on serum when blood samples are unavailable.

Publications

Pomari E et al, Pathogens, 2020 https://doi.org/10.3390/pathogens9060478

Funding

Fondo Ricerca Corrente, Italian Ministry of Health

Macro-project 3: Evaluation of drug efficacy for Covid-19

Cover. High-dose ivermectin for early treatment of COVID-19

- Project coordinator: DITM
- P.I. Zeno Bisoffi
- Start date: 2020
- End date: 2022

Background and purpose

High concentrations of ivermectin demonstrated antiviral activity against SARS-CoV-2 in vitro. The aim of this study was to assess the safety and efficacy of high-dose ivermectin in reducing viral load in individuals with early SARS-CoV-2 infection.

Methods

This was a randomised, double-blind, multicentre, phase II, dose-finding, proof-of-concept clinical trial. Participants were adults recently diagnosed with asymptomatic/ oligosymptomatic SARS-CoV-2 infection. Primary outcomes were a) definition of ivermectin safety, versus placebo (Arm A) at the highest doses ever used in humans: 600 (Arm B) or 1200 (Arm C) µg/kg in participants with initial, asymptomatic or oligosymptomatic SARS- CoV-2 infection and b) decrease of the viral load of SARS-CoV-2 at Day 7 after administration of high-dose ivermectin.

Results

From 31 July 2020 to 26 May 2021, 32 participants were randomised to arm A, 29 to

arm B and 32 to arm C. No SADRs were registered. Mean (S.D.) log_{10} viral load reduction was 2.9 (1.6) in arm C, 2.5 (2.2) in arm B and 2.0 (2.1) in arm A, with no significant differences (P = 0.099 and 0.122 for C vs. A and B vs. A, respectively). High-dose ivermectin was safe but did not show efficacy to reduce viral load.

Primary efficacy endpoint of viral load in the evaluable analysis set, overall and by study arm

	Arm A (N = 29)	Arm B (N = 28)	Arm C (N = 30)	Overall (N = 87)
SARS-CoV-2 viral load at baseline (log_{10})				
Mean ± S.D.	4.3 ± 1.3	4.3 ± 1.2	4.5 ± 1.2	4.4 ± 1.2
Median (IQR)	4.4 (3.5–5.2)	4.3 (3.8–5.1)	4.4 (4.0–5.2)	4.4 (3.8–5.2)
Range	1.7–6.6	2.3–6.6	2.1–7.0	1.7–7.0
Missing	1	0	1	2
SARS-CoV-2 viral load at Day 7 (log_{10})				
Mean ± S.D.	2.2 ± 1.5	1.9 ± 1.6	1.6 ± 1.2	1.9 ± 1.4
Median (IQR)	2.3 (1.1–2.8)	1.5 (0.9–2.5)	1.6 (0.9–2.5)	1.7 (0.9–2.7)
Range	0.0–6.7	0.0–5.2	0.0–5.4	0.0–6.7
Differences in viral load decline from baseline to 7 days				
Mean ± S.D.	2.0 ± 2.1	2.5 ± 2.2	2.9 ± 1.6	2.5 ± 2.0
Median (IQR)	2.6 (1.6–3.2)	3.1 (2.3–4.1)	3.1 (1.8–4.1)	2.8 (1.7–3.7)
Range	−4.8 to 4.9	−2.9 to 4.9	−0.2 to 5.5	−4.8 to 5.5
Missing	1	0	1	2
Effect size				
Arm B vs. arm A				0.21
Arm C vs. arm A				0.48
Shapiro–Wilk test P-value (test for normal distribution)				
Arm B vs. arm A				<0.0001
Arm C vs. arm A				<0.0001
Wilcoxon exact P-value				
Arm B vs. arm A				0.122
Arm C vs. arm A				0.099
T-test P-value				
Arm B vs. arm A				0.429
Arm C vs. arm A				0.078

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S.D., standard deviation; IQR, interquartile range.
NOTE: Arm A, placebo; arm B, ivermectin 600 μg/kg + placebo for 5 days; and arm C, ivermectin 1200 μg/kg for 5 days.

Publications

Buonfrate D, et al. Int J Antimicrob Agents. 2022. https://doi.org/10.1016/j.ijantimicag.2021.106516

Buonfrate, D., Bisoffi, Z., Chest J, 2021. https://doi.org/10.1016/j.chest.2021.03.003

Funding

Fondo Ricerca Corrente, Italian Ministry of Health. Grant from Alpine Lions Cooperation

Anakinra. Early treatment of COVID-19 with anakinra

- Project Coordinator: National and Kapodistrian University of Athens, Greece
- DITM P.I. Andrea Angheben
- Other institutions involved: Several health institutions from Greece and Italy.
- Start date: 2020
- End date: 2021

Background and purpose

Early increase of soluble urokinase plasminogen activator receptor (suPAR) serum levels is indicative of increased risk of progression of coronavirus disease 2019 (COVID-19) to respiratory failure. The main purpose of the study was to evaluate the efficacy and safety of early initiation of anakinra treatment in hospitalized patients with moderate or severe COVID-19. The primary objective was to evaluate the efficacy and safety of early anakinra administration on the 11-point ordinal WHO-CPS on day 28 from the start of treatment. At day 28, the adjusted proportional odds of having a worse clinical status (assessed by the 11-point World Health Organization Clinical Progression Scale (WHO-CPS)) with anakinra, as compared to placebo, was 0.36 (95% confidence interval 0.26-0.50). The median WHO-CPS decrease on day 28 from baseline in the placebo and anakinra groups was 3 and 4 points, respectively (odds ratio (OR) = 0.40, P < 0.0001); the respective median decrease of Sequential Organ Failure Assessment (SOFA) score on day 7 from baseline was 0 and 1 points (OR = 0.63, P = 0.004). Twenty-eight-day mortality decreased (hazard ratio = 0.45, P = 0.045), and hospital stay was shorter.

Methods

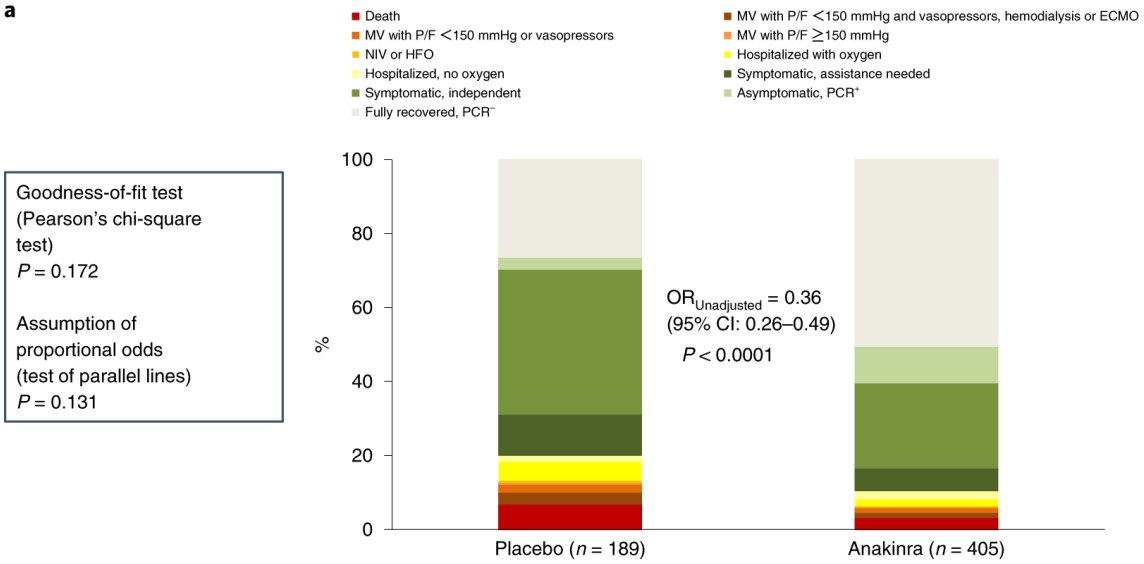
Double-blind, randomized controlled trial to evaluate the efficacy and safety of anakinra, an IL-1 / inhibitor, in 594 patients with COVID-19 at risk of progressing to respiratory failure as identified by plasma suPAR ≥6 ng ml-1, 85.9% (n = 510) of whom were receiving dexamethasone.

Results

At day 28, the adjusted proportional odds of having a worse clinical status (assessed by the 11-point World Health Organization Clinical Progression Scale (WHO-CPS)) with anakinra, as compared to placebo, was 0.36 (95% confidence interval 0.26-0.50). The median WHO-CPS decrease on day 28 from baseline in the placebo and anakinra groups was 3 and 4 points, respectively (odds ratio (OR) = 0.40, P < 0.0001); the

respective median decrease of Sequential Organ Failure Assessment (SOFA) score on day 7 from baseline was 0 and 1 points (OR = 0.63, P = 0.004). Twenty-eight-day mortality decreased (hazard ratio = 0.45, P = 0.045), and hospital stay was shorter.

a



b

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Group of treatment (Anakinra vs placebo)	0.36	0.26–0.49	<0.0001	0.36	0.26–0.50	<0.0001
Intake of dexamethasone (Yes/No)	1.90	1.28–2.83	0.002	1.49	0.59–3.80	0.395
Severe COVID-19 by WHO (Yes/No)	1.95	1.31–2.90	0.001	1.29	0.51–3.27	0.582
BMI >30 kg m^{-2} (Yes/No)	1.27	0.87–1.61	0.267	1.10	0.81–1.50	0.530
Country (Italy vs Greece)	1.18	0.74–1.88	0.482	1.25	0.77–2.03	0.350

***a**, Distribution of the WHO-CPS scores at day 28 of patients allocated to treatment with placebo and to treatment with anakinra. Comparison is done by unadjusted ordinal regression analysis; the ORs of the 95% CIs are provided. The exact P value of the unadjusted ordinal regression analysis is 3.6×10^{-10}. The two tests of the assumptions of the ordinal regression analysis are also provided.*

***b**, Univariate and multivariate ordinal regression analysis of the WHO-CPS scores at day 28. The exact P value of the effect of anakinra versus placebo treatment in the multivariate analysis is 7.7×10^{-10}. Covariates entered in the multivariate model were those used for stratified randomization according to advice received from the COVID-ETF. ECMO, extracorporeal membrane oxygenation; P/F, respiratory ratio*

Publications

Kyriazopoulou E., et al. Nat Med., 2021. https://doi.org/10.1038/s41591-021-01499-z

Cattaneo P., Microorganisms, 2021. https://doi.org/10.3390/microorganisms9071393

Funding

Fondo Ricerca Corrente, Italian Ministry of Health. Hellenic Institute for the Study of Sepsis, Greece.

Tocilizumab. Tocilizumab vs Standard Care in COVID-19 pneumonia.

- Project Coordinator: Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy.
- DITM P.I. Andrea Angheben
- Other institutions involved: Several health institutions from Italy.
- Start date: 2020
- End date: 2021

Background and purpose

The coronavirus disease 2019 (COVID-19) pandemic is threatening billions of people worldwide. Tocilizumab has shown promising results in retrospective studies in patients with COVID-19 pneumonia with a good safety profile. Purpose of this study was evaluate the effect of early tocilizumab administration vs standard therapy in preventing clinical worsening in patients hospitalized with COVID-19 pneumonia.

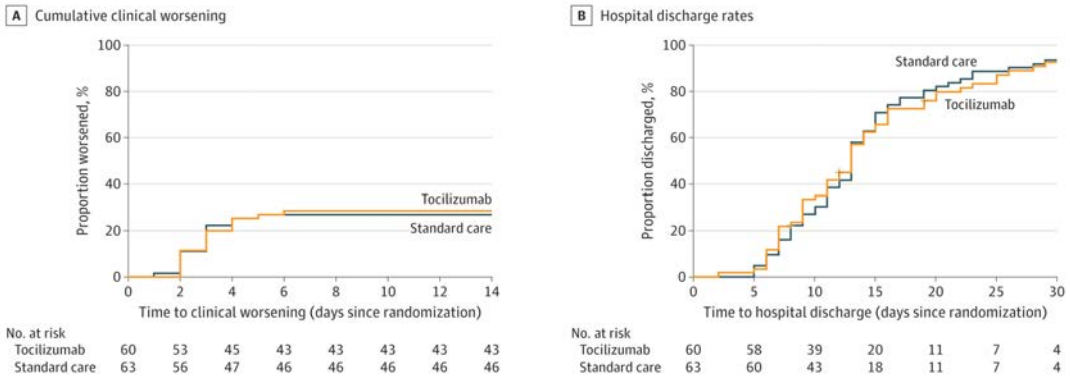
Methods

Prospective, open-label, randomized clinical trial that randomized patients hospitalized between March 31 and June 11, 2020, with COVID-19 pneumonia to receive tocilizumab or standard of care in 24 hospitals in Italy. Cases of COVID-19 were confirmed by polymerase chain reaction method with nasopharyngeal swab. Eligibility criteria included COVID-19 pneumonia documented by radiologic imaging, partial pressure of arterial oxygen to fraction of inspired oxygen (Pao2/Fio2) ratio between 200 and 300 mm Hg, and an inflammatory phenotype defined by fever and elevated C-reactive protein. Patients in the experimental arm received intravenous tocilizumab within 8 hours from randomization (8 mg/kg up to a maximum of 800 mg), followed by a second dose after 12 hours. Patients in the control arm received supportive care following the protocols of each clinical center until clinical worsening and then could receive tocilizumab as a rescue therapy. he primary composite outcome was defined as entry into the intensive care unit with invasive mechanical ventilation, death from

all causes, or clinical aggravation documented by the finding of a Pao2/Fio2 ratio less than 150 mm Hg, whichever came first.

Results

126 patients were randomized (60 to the tocilizumab group; 66 to the control group), 123 were available for the intention-to-treat analyses. Seventeen patients of 60 (28.3%) in the tocilizumab arm and 17 of 63 (27.0%) in the standard care group showed clinical worsening within 14 days since randomization (rate ratio, 1.05; 95% CI, 0.59-1.86). Two patients in the experimental group and 1 in the control group died before 30 days from randomization, and 6 and 5 patients were intubated in the 2 groups, respectively. The trial was prematurely interrupted after an interim analysis for futility. No benefit on disease progression was observed.



Kaplan-Meier estimates of cumulative clinical worsening (A) and hospital discharge (B).

Publications

Salvarani C., et al, JAMA Int. Med. 2020. https://doi.org/10.1001/jamainternmed.2020.6615

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

Macro-project 4: Clinical and epidemiological characteristics of Covid-19

CovidVR. A longitudinal, follow-up study of SARS-CoV-2 infection, Verona, Italy

- Project Coordinator: IRCCS (DITM and Unit of Pneumology)
- P.I. Zeno Bisoffi , Carlo Pomari
- Other institutions involved: University of Verona, Italy. Azienda Ospedaliera Universitaria, Verona, Italy. USL 9 of Veneto Region, Verona, Italy.
- Start date: 2021
- End date: 2022

Background and purpose

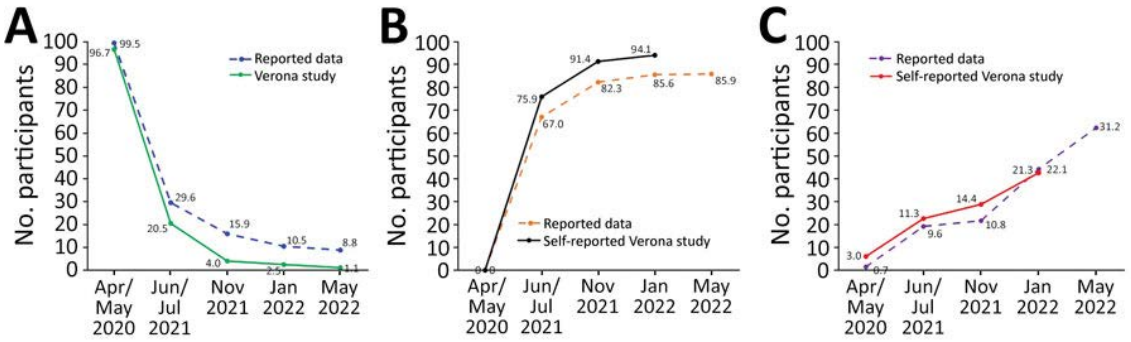
Data on SARS-CoV-2 infection are usually obtained from routine health sources that are not representative of the general population. We aimed to obtain a more objective assessment of the real prevalence of the infection and its evolution over time.

Methods

In April and May, 2020, we used random sampling to estimate the prevalence of severe acute respiratory syndrome coronavirus 2 infection in Verona, Italy. We then performed a follow-up of the baseline prevalence study in three phases over 2 years, ending in May, 2022.

Results

In May, 2020, of 1,515 participants, 2.6% tested positive by serologic assay and 0.7% by reverse transcription PCR. We used latent class analysis to estimate a 3.0% prevalence of infection, 5 times the official figures, and 1.9% death rate, 1/5th of the official figures. At the end of the follow-up (May 2022), only 1% of the city population had never been infected or vaccinated (or was completely naïve), versus 8.8% officially reported. The pandemic seems to have entered a phase in which we can be cautiously optimistic. It remains crucial to protect the frail and elderly subjects, while a cautious relaxation of restrictions for the general population seems justified, and repeated boosters for non-frail subjects might not be necessary.



Reported and sampling data for SARS-CoV-2, Verona, Italy, May 2020–2022. Comparison is shown between official (reported) and Verona study proportions of naive (A), vaccinated (B), and infected (C) persons. Values along data lines indicate cumulative incidence.

Publications

Guerriero M. et al, BMJ Open, 2020. https://doi.org/10.1136/bmjopen-2020-040036

Guerriero M et al, Em. Inf. Dis. 2021. https://doi.org/10.3201/eid2701.202740

Bisoffi Z. et al, Em. Inf. Dis. 2023. https://doi.org/10.3201/eid2904.221268

Funding

Fondo Ricerca Corrente, Italian Ministry of Health, Progetto COVID Ricerca Finalizza-ta-2020-12371675 and European Union funding within the NextGenerationEU-MUR PNRR Extended Partnership initiative on Emerging Infectious Diseases (Project no. PE00000007, INF-ACT).

SARSload. Overall decrease in SARS-CoV-2 viral load and reduction in clinical burden

- Project Coordinator: DITM
- P.I. Chiara Piubelli
- Start date: 2020
- End date: 2021

Background and purpose

In Italy the burden of patients with coronavirus disease 2019 (COVID-19) gradually

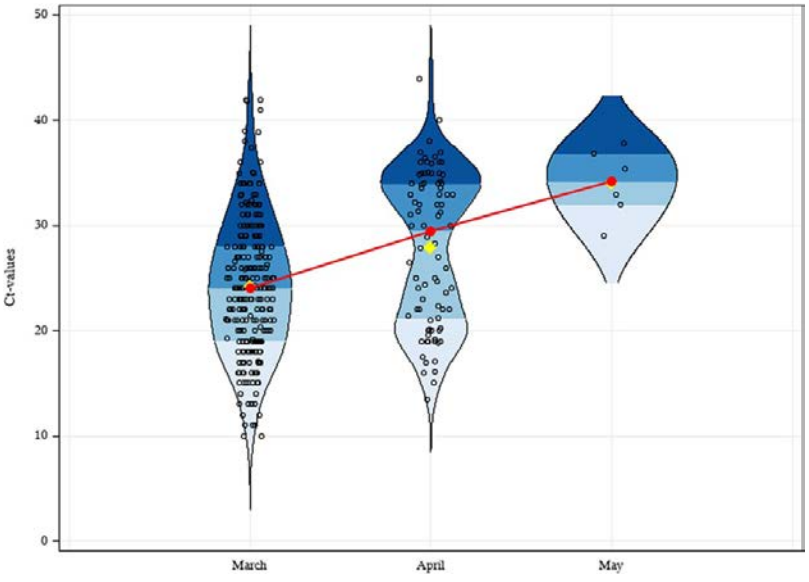
decreased from March to the end of May. In this work we aimed to evaluate a possible association between the severity of clinical manifestations and viral load over time during the epidemiological transition from high-to low-transmission settings.

Methods

We reviewed the cases of COVID-19 diagnosed at the emergency room of our hospital, retrieving the proportion of patients admitted to the intensive care unit. A raw estimation of the viral load was done evaluating the Ct (cycle threshold) trend obtained from our diagnostic reverse transcriptase real-time PCR test.

Results

The proportion of patients requiring intensive care significantly decreased from 6.7% (19/281) in March to 1.1% (1/86) in April, and to none in May (Fisher's test p 0.0067). As for viral load, we observed a trend of Ct increasing from a median value of 24 (IQR 19-29) to 34 (IQR 29-37) between March and May, with a statistically significant difference between March and April (p 0.0003). Conclusions: We observed a reduction over time in the proportion of patients with COVID-19 requiring intensive care, along with decreasing median values of viral load.



Violin plot showing the distribution of 373 COVID-19 cases, 281 subjects in March (median = 24, Q1 = 19, Q3 = 29), 86 in April (median = 30, Q1 = 21, Q3 = 34) and six in May (median = 34, Q1 = 29, Q3 = 37). Quartiles are represented by blue shades, means by yellow points, and medians by red dots. The red line shows the trend line.

Publications

Piubelli C. et al. Clinical Micr. and Infection, 2021. https://doi.org/10.1016/j.cmi.2020.10.006

Funding

Fondo Ricerca Corrente, Italian Ministry of Health

CovidIBD. A Seroprevalence Study of Anti-SARS-CoV-2 Antibodies in Patients with Inflammatory Bowel Disease

- Project Coordinator: IRCCS (DITM, Unit of Gastroenterology, Unit of Laboratory)
- DITM P.I. Federico Gobbi
- Start date: 2020
- End date: 2021

Background and purpose

Studies have shown a lower prevalence of anti-SARS-CoV-2 antibodies in patients with inflammatory bowel disease (IBD), including amongst those receiving biological therapy. Aims were to determine the seroprevalence of anti-SARS-CoV-2 antibodies in IBD patients and to assess any association between seropositivity and IBD characteristics.

Methods

Serum from adult IBD patients was prospectively collected between December 2020 and January 2021 and analyzed for anti-SARS-CoV-2 antibodies. Information about IBD characteristics and SARS-CoV-2 exposure risk factors was collected and analyzed. Serum from non-IBD healthcare workers formed the control group.

Results

311 IBD patients on biologics and 75 on mesalazine were enrolled. Ulcerative colitis (UC) extension ($p < 0.001$), Crohn's disease (CD) phenotype ($p = 0.009$) and use of concomitant corticosteroids ($p < 0.001$) were significantly different between the two IBD groups. Overall seroprevalence among IBD patients was 10.4%, and in control group 13.0% ($p = 0.145$). Only a close contact with SARS-CoV-2 positive individuals and the use of non-FFP2 masks were associated with a higher likelihood of seropositivity amongst IBD patients. Conclusion: In IBD patients, the prevalence of anti-SARS-CoV-2 antibodies is not determined by their ongoing treatment. Disease-related characteristics are not associated with a greater risk of antibody seropositivity.

Publications

Di Ruscio M. et al, Medicina, 2021. https://doi.org/10.3390/medicina57101048

Funding

Fondo Ricerca Corrente, Italian Ministry of Health

CovidCohort. Study of anti-SARS-CoV-2 immunity pre- and post-vaccination in health workers with and without a previous infection.

- Project Coordinator: DITM
- P.I Zeno Bisoffi
- Start date: 2021
- End date: ongoing

Starting with 1st January, 2021, a cohort of vaccinated health workers of our IRCCS was constituted. All consenting HCW supplied blood samples upon administration of the first (T0) and the second (T1) dose of vaccine, and 2–3 weeks after the second dose (T2). Smaller groups from the same cohort were also followed up after subsequent doses.

From the main cohort, different sub-projects were developed.

CovidCohort1. Antibody response induced by the BNT162b2 mRNA COVID-19 vaccine in a cohort of health-care workers, with or without prior SARS-CoV-2 infection: a prospective study

- Project Coordinator: DITM
- P.I. Zeno Bisoffi
- Start date: 2021
- End date: 2021

Background and purpose

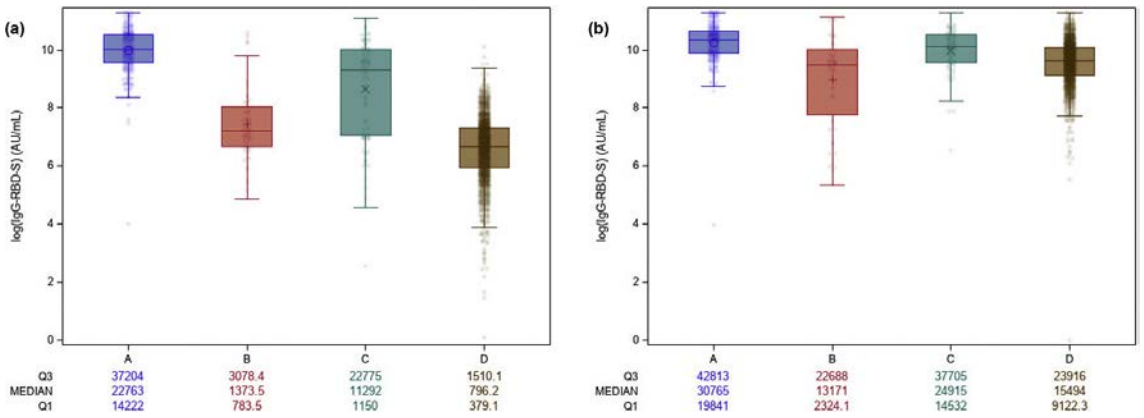
Real-world data demonstrating the effectiveness of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are badly needed. Purpose of this study was to assess the antibody response to BNT162b2 mRNA COVID-19 vaccine in a cohort of health-care workers (HCW), comparing individuals with previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and SARS-CoV-2-naive individuals.

Methods

HCW were tested at T0 (day of first dose), T1 (day of second dose) and T2 (2–3 weeks after second dose) for IgG anti-nucleocapsid protein, IgM anti-spike protein and IgG anti-receptor binding domain (IgG-RBD-S). The antibody response was compared between four main groups: group A, individuals with previous infection and positive antibodies at baseline; group B, individuals with the same history but negative antibodies; group C, individuals with no infection history but positive antibodies; group D, naive individuals. Repeated measures analysis was used to compare results over time-points.

Results

1935 HCW were included. Median IgG-RBD-S titre was significantly higher for group A (232 individuals) than for group B (56 individuals) both at T1 (A: 22 763 AU/mL, B: 1373 AU/mL, p 0.0003) and T2 (A: 30 765 AU/mL, B: 13 171 AU/mL, p 0.0038) and for group D (1563 individuals; 796 AU/mL, at T1; 15 494 AU/mL, at T2, $p < 0.0001$ for both time-points). T1 values of group A were also significantly higher than T2 values of group D ($p < 0.0001$). HCW infected in March showed a significantly stronger than those infected in November (T1: 18 499 AU/mL, T2: 23 210 AU/mL, $p < 0.0001$ for both time-points). In conclusion, individuals with past SARS-CoV-2 infection had a strong antibody response after one single vaccine shot. A single dose might be sufficient for this group, regardless of the time elapsed since infection; however, the clinical correlation with antibody response needs to be studied.



Dynamics of IgG-RBD-S antibodies over time in the different groups. (a) Values at T1; (b) values at T2. Group A: Seropositive exCOVID-19 health-care workers (HCW); Group B: Seronegative exCOVID-19 HCW; Group C: HCW qith Suspected previous infections; Group D: Naive individuals. The values below the figure are reported as medians of IgG-RBD-S (AU/mL) and interquartile range. The figures have been created in logarithmic (log 10) scale.

Publications

Buonfrate D., et al. Clinical Micr. and Infection, 2021 https://doi.org/10.1016/j.cmi.2021.07.024

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

Concomitant. Antibody response in individuals infected with SARS-CoV-2 early after the first dose of the BNT162b2 mRNA vaccine

- Project Coordinator: DITM
- P.I. Federico Gobbi
- Other institutions involved: University of Padova, Italy.
- Start date: 2021
- End date: 2021

Background and purpose

Conceivably, SARS-CoV-2 infection following the first vaccine dose might also act

as a booster. However, information about the levels of protective antibodies in these individuals are lacking and there are no indications about the appropriateness of a second dose of vaccine in individuals who were infected with SARS-CoV-2 after having received the first dose. We investigated the dynamics of antibody response to SARS-CoV-2 in HCWs who were infected within 14 days after the first dose of BNT162b2 mRNA vaccine in comparison with the response to vaccination in naïve HCWs and in those with prior infection.

Methods

The anti-SARS-CoV-2 antibody response in this group of HCWs (group A: concomitant infection) was compared with that observed in other groups: i.e., HCWs who got infected from March 2020 to November 2020 and were vaccinated in January 2021 (group B: prior infection, ≥ 2 months, n = 55); HCWs who got infected in December 2020 and had vaccination postponed > 1 month (group C: prior infection, < 2 months, n = 26), and naïve HCWs, who were regularly vaccinated in January 2021 (group D: naïve, n = 55). Group A received the second vaccine dose a median of 75 days after dose 1; groups B, C, and D received the second dose 21 days after the first dose. In group A, SARS-CoV-2 infection was diagnosed a median of 8 days after the first vaccine dose. All study subjects were tested for anti-SARS-CoV-2 spike receptor-binding domain (RBD) IgG antibodies and neutralizing antibodies. Testing was performed upon administration of the first (T0) and the second (T1) vaccine doses, and 2 to 3 weeks after the second dose (T2). For group A, T1 was set on day 38 after the first vaccine dose.

Results

This study demonstrated that the titers of SARS-CoV-2 RBD-binding IgG and neutralizing antibodies induced by vaccination with BNT162b2 were significantly higher in HCWs infected with SARS-CoV-2 ≤ 14 days after the first vaccine dose than in naïve subjects, but significantly lower than in HCWs infected before vaccination. Thus, while recommending a single dose for individuals who were infected months before vaccination, the same approach might not be appropriate for those who are diagnosed with the infection soon after the first dose of vaccines.

Publications

Gobbi F. et al. Journal of Infection, 2021. https://doi.org/10.1016/j.jinf.2021.08.008

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

AntibodyInf. Antibody response in individuals with prior SARS-CoV-2 infection

- Project Coordinator: DITM
- P.I. Federico Gobbi
- Other institutions involved: University of Padova, Italy.
- Start date: 2021
- End date: 2021

Background and purpose

Although antibody levels progressively decrease following SARS-CoV-2 infection, the immune memory persists for months. Thus, individuals who naturally contracted SARS-CoV-2 are expected to develop a more rapid and sustained response to COVID-19 vaccines than naïve individuals.

Methods

In this study, we analyzed the dynamics of the antibody response to the BNT162b2 mRNA COVID-19 vaccine in six healthcare workers who contracted SARS-CoV-2 in March 2020, in comparison to nine control subjects without a previous infection.

Results

Overall, the titers of neutralizing antibodies were markedly higher in response to the vaccine than after natural infection. In all subjects with pre-existing immunity, a rapid increase in anti-spike receptor-binding domain (RBD) IgG antibodies and neutralizing antibody titers was observed one week after the first dose, which seemed to act as a booster. Notably, in previously infected individuals, neutralizing antibody titers 7 days after the first vaccine dose were not significantly different from those observed in naïve subjects 7 days after the second vaccine dose. These results suggest that, in previously infected people, a single dose of the vaccine might be sufficient to induce an effective response.

Publications

Gobbi F. et al. Viruses 2021. https://doi.org/10.3390/v13030422

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

CovidIgA. Serology study after BTN162b2 vaccination in participants previously infected versus naïve

- Project Coordinator: University of Verona, Italy.
- DITM P.I. Chiara Piubelli
- Other institutions involved: IRCCS San Raffaele, Milan, Italy. University of Trento, Italy. Covi2 Technologies Srl, Novara, Italy
- Start date: 2021
- End date: 2022

Background and purpose

The antibody response to SARS-CoV-2 mRNA vaccines in individuals with waning immunity generated by a previous SARS-CoV-2 infection, as well as the patterns of IgA and IgM responses in previously infected and in naïve individuals are still poorly understood. We aimed at assessing IgG and IgM and IgA antibodies, as well as the neutralizing activity, after SARS-CoV-2 vaccination in previously infected/not infected health workers.

Methods

We performed a serology study in a cohort of BTN162b2 mRNA vaccine recipients who were immunologically naïve (N, n = 50) or had been previously infected with SARS-CoV-2 (P.I., n = 51) during the first (n = 25) or second (n = 26) pandemic waves in Italy, respectively. We measured IgG, IgM and IgA antibodies against the SARS-CoV-2 Spike (S) and IgG against the nucleocapsid (N) proteins, as well as the neutralizing activity of sera collected before vaccination, after the first and second dose of vaccine.

Results

Most P.I. individuals from the first pandemic wave who showed declining antibody titres responded to the first vaccine dose with IgG-S and pseudovirus neutralization titres that were significantly higher than those observed in N individuals after the second vaccine dose. In all, a single dose induced a potent IgA response that was not associated with serum neutralization titres. The response to a single dose of vaccine in P.I. individuals is more potent than that observed in N individuals after two doses. Vaccine-induced IgA are not associated with serum neutralization.

Publications

Dalle Carbonare L., et al. Communications medicine 2021. https://doi.org/10.1038/s43856-021-00039-7

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

S&Co. Sex and COVID-19 investigational multi-center study.

- Project Coordinator: DITM and University of Florida, USA.
- DITM P.I. Anna Beltrame, Lucia Moro
- Start date: 2020
- End date: 2021
- Other institutions involved: IRCCS Humanitas, Milan, Italy. University of Trento, Italy. Ospedale San Gerardo, Monza, Italy
- Start date: 2020
- End date: 2021

Background and purpose

Understanding the cause of sex disparities in COVID-19 outcomes is a major challenge. We investigate sex hormone levels and their association with outcomes in COVID-19 patients, stratified by sex and age.

Methods

This observational, retrospective, cohort study included 138 patients aged 18 years or older with COVID-19, hospitalized in Italy between February 1 and May 30, 2020. The association between sex hormones (testosterone, estradiol, progesterone, dehydroepiandrosterone) and outcomes (ARDS, severe COVID-19, in-hospital mortality) was explored in 120 patients aged 50 years and over. STROBE checklist was followed.

Results

Median age was 73.5 years; 55.8% were male. In older males, testosterone was lower if ARDS and severe COVID-19 were reported than if not. Deceased males had lower testosterone and higher estradiol than survivors. Testosterone was negatively associated with ARDS, severe COVID-19, and in-hospital mortality, regardless of potential confounders, though confirmed only in the regression model on males. Higher estradiol was associated with a higher probability of death, confirmed in both sex models. In males, higher testosterone seems to be protective against any considered outcome. Higher estradiol was associated with a higher probability of death in both sexes.

Publications

Beltrame A. et al, Frontiers in immunology, 2022. https://doi.org/10.3389/fimmu.2022.834851

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

UnCover. Unravelling Data for Rapid Evidence-Based Response to COVID-19

- Project coordinator: Antwerp University Hospital, Belgium
- DITM P.I.: Dora Buonfrate
- Other institutions involved: Antwerp University Hospital (Uza), Fundacion Investigacion Hospitales, Universidad Politecnica De Madrid, Universidad De Navarra, Universidade Do Porto, Technological University Dublin, University College Cork, Universitatea De Medicina Si Farmacie Iuliu Hatieganu Cluj-Napoca, Universitatea De Medicina Si Farmacie Grigore T Popa Din Iasi, Luxembourg Institute Of Health, Universidade Catolica Portuguesa, Trnavska Univerzita V Trnave, Instituto Politecnico De Coimbra, Servicio Madrileño De Salud - Fundacion Investigacion Biomedica Hospital Universitario La Princesa, Instituto Investigacion Sanitaria Fundación Jimenez Diaz, Panepistimio Thessalias, Universitetet I Sorost-Norge, Sciensano, Hrvatski Zavod Za Javno Zdravsto, Institut Za Antropologiju, Baskent University, St Mary's University Twickenham, Azienda Ulss 6 Euganea, Korea University, University Of South Florida, Universidad De Antioquia, Associacao Pro Ensino Superior Em Novo Hamburgo, Univerzitet U Sarajevu

- Start date: 2020
- End date: ongoing

Background and purpose

COVID-19 pandemic required a colossal effort from health systems, and hospitals across Europe. unCoVer aspires to use these data and to bring complementary expertise together to address the still urgent questions regarding the elevated risks observed among COVID-19 patients with chronic comorbidities to inform more effective public health strategies and medical treatments.

Methods

unCoVer will 1)ring together expertise and data to synchronize research on COVID-19 pandemic. 2) facilitate the access of COVID-19-related RWD to fully exploit routinea-ta. 3) identify data gaps and seek synergies with complementary existing and planned clinical databases. 4) provide a platform for the use of dissimilar data sources. 5) bring together expertise on the use of advanced computational, epidemiological and biostatistical methods, underlying drivers of COVID-19 prognosis, the safety and effectiveness of treatments, and sequelae, as well as the impact of COVID-19 in health system resources. 6) broadcast the use and results of the platform.

Publications

Penalvo JL et al. BMJ Open 2021. https://doi.org/10.1136/bmjopen-2021-055630

Funding

EC (Horizon 2020)

Macro-project 5: Improving the diagnosis and the pathophysiology knowledge of SARS-CoV-2

COVID_Diag. Accuracy of molecular and serological tests for COVID-19

- Project Coordinator: DITM
- P.I. Zeno Bisoffi

- Other institutions involved: University of Verona, Italy.
- Start date: 2020
- End date: 2020

Background and purpose

We assessed the sensitivity, specificity and positive and negative predictive value (PPV and NPV) of molecular and serological tests for the diagnosis of SARS-CoV-2 infection.

Methods

A total of 346 patients were enrolled in the emergency room. We evaluated three Reverse Transcriptase-real time PCRs (RT-PCRs) including six different gene targets, five serologic rapid diagnostic tests (RDT) and one ELISA. The final classification of infected/non-infected patients was performed using Latent Class Analysis combined with clinical re-assessment of incongruous cases.

Results

24.6% of patients were classified as infected. Molecular test RQ-SARS-nCoV-2 had the highest performance: 91.8% sensitivity, 100% specificity, 100.0% PPV and 97.4% NPV respectively. Considering single genes, *S* and *RdRp* of RQ-SARS-nCoV-2 had the highest sensitivity (94.1%). The in-house *RdRp* presented the lowest sensitivity (62.4%). Specificity ranged from 99.2% for in-house *RdRp* and *N2* to 95.0% for *E*. PPV ranged 97.1% of *N2* to 85.4% of *E* and NPV from 98.1% of *S* to 89.0% of in-house *RdRp*. All serological tests had < 50% sensitivity and low PPV and NPV. Conclusion: Molecular tests for SARS-CoV-2 infection showed excellent specificity, but significant differences in sensitivity. Serological tests have limited utility in a clinical context.

Publications

Bisoffi Z. et al, diagnostics, 2020. https://doi.org/10.3390/diagnostics10090669

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

ImmunoPhen. Immunophenotype analysis in patients with SARS-CoV-2 infection

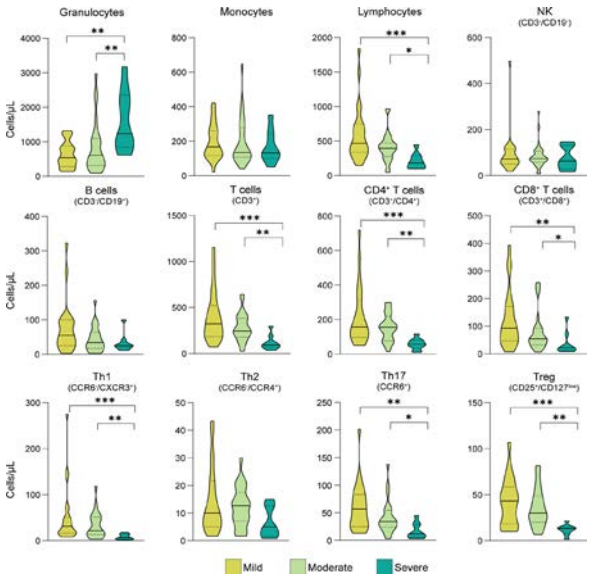
- Project Coordinator: DITM
- P.I. Sara Caldrer
- Start date: 2020
- End date: 2021

Background and purpose

The host immune response has a prominent role in the progression and outcome of SARS-CoV-2 infection. Lymphopenia has been described as an important feature of SARS-CoV-2 infection and has been associated with severe disease manifestation. Lymphocyte dysregulation and hyper-inflammation have been shown to be associated with a more severe clinical course; however, a T cell subpopulation whose dysfunction correlate with disease progression has yet to be identified.

Methods

We performed an immuno-phenotypic analysis of T cell sub-populations in peripheral blood from patients affected by different severity of COVID-19 (n=60) and undergoing a different clinical evolution. Clinical severity was established based on a modified WHO score considering both ventilation support and respiratory capacity (PaO2/FiO2 ratio). The ability of circulating cells at baseline to predict the probability of clinical aggravation was explored through multivariate regression analyses.



*Immunophenotypic analysis in COVID-19 patients classified according to the severity of the disease. Distribution of the absolute number of cells (expressed as cells/µl of blood) across the three groups of COVID-19 patients suffering from different disease severity, i.e. mild or score 4 (n = 23), moderate or score 5 (n = 28), severe or score ≥6 (n = 9), established according to a modified WHO classification (20). Statistical significance, set at p-value <0.05, was assessed using the Kruskal-Wallis test followed by the Dunn's post-test and Bonferroni correction for multiple comparisons. *p < 0.05; **p < 0.01; ***p < 0.001*

Results

Severe COVID-19 patients had reduced circulating T cell subsets, especially CD4+ T, Th1, and regulatory T cells. Peripheral T cells correlated with disease severity. CD4+ T cell subsets showed an important significant association with clinical evolution, with patients presenting markedly decreased regulatory T cells at baseline having a significantly higher risk of aggravation. The combination of gender and regulatory T cells allowed distinguishing between improved and worsened patients with an AUC of 82%. The present study demonstrates the association between CD4+ T cell dysregulation and COVID-19 severity and progression. Regulatory T cells assessment after hospital admission could allow better clinical stratification.

Publications

Caldrer S. et al, Frontiers in immunology, 2022. https://doi.org/10.3389/fimu.2021.789735

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

SARS-CoV-2_ddPCR. Assessment of the direct quantitation of SARS-CoV-2 by droplet digital PCR

- Project Coordinator: DITM
- P.I. Elena Pomari
- Other institutions involved: University of Verona, Italy. ULSS3 Venetian, Venice, Italy.
- Start date: 2020
- End date: 2020

Background and purpose

Droplet digital PCR (ddPCR) is a sensitive and reproducible technology widely used for quantitation of several viruses. The aim of this study was to evaluate the 2019-nCoV CDC ddPCR Triplex Probe Assay (BioRad) performance, comparing the direct quantitation of SARS-CoV-2 on nasopharyngeal swab with the procedure applied to the extracted RNA. Moreover, two widely used swab types were compared (UTM 3

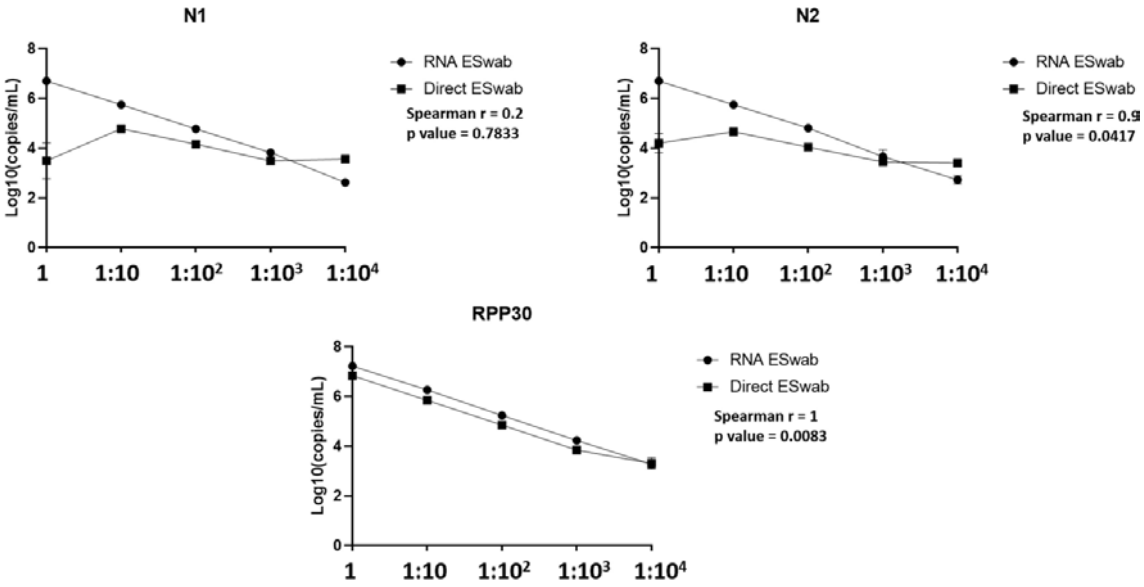
mL and ESwab 1 mL, COPAN). A total of 50 nasopharyngeal swabs (n = 25 UTM 3 mL and n = 25 ESwab 1 mL) from SARS-CoV-2 patients, collected during the pandemic at IRCCS Sacro Cuore Don Calabria Hospital (Veneto Region, North-East Italy), were used for our purpose.

Methods

After heat inactivation, an aliquot of swab medium was used for the direct quantitation. Then, we compared the direct method with the quantitation performed on the RNA purified from nasopharyngeal swab by automated extraction.

Results

The direct approach achieved generally equal RNA copies as the extracted RNA. Results with direct quantitation were more accurate on ESwab with 93% sensitivity and 100.00% specificity for N1 and N2. On UTM we observed a higher rate of discordant results for N1 and N2. The human internal amplification control (RPP30) showed 100% of both sensitivity and specificity independent of swabs and approaches. In conclusion, our approach resulted in an efficient quantitation. Special care needs to be taken on potential bias due to the conservation of samples and to the heating treatment, as we used thawed and heat inactivated material. Further studies on a larger cohort of samples are warranted to evaluate the clinical value of this direct approach.



Results of the limit of detection analysis on ESwab.

Publications

Deiana M. et al, Scientific Reports, 2020. https://doi.org/10.1038/s41598-020-75958-x

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

SARS_EpiMap. SARS-CoV-2 Epitope Mapping on Microarrays

- Project Coordinator: National Research Council, Italy
- DITM P.I. Chiara Piubelli
- Other institutions involved: University of Padova, Italy.
- Start date: 2020
- End date: 2021

Background and purpose

Peptide microarrays represent appealing tools, as they allow the rapid screening of hundreds to thousands different peptides immobilized in spatially ordered patterns of spots on solid supports. This approach was used to provide a first landscape of B-cell epitopes in the serum of 10 coronavirus disease of 2019 (Covid-19) patients.

Methods

A workflow for rapid SARS-CoV-2 epitope discovery on peptide microarrays is herein reported. The process started with a proteome-wide screening of immunoreactivity based on the use of a high-density microarray followed by a refinement and validation phase on a restricted panel of probes using microarrays with tailored peptide immobilization through a click-based strategy. Progressively larger, independent cohorts of Covid-19 positive sera were tested in the refinement processes, leading to the identification of immunodominant regions on SARS-CoV-2 spike (S), nucleocapsid (N) protein and Orf1ab polyprotein.

Results

A summary study testing 50 serum samples highlighted an epitope of the N protein (region 155–71) providing good diagnostic performance in discriminating Covid-19

positive vs. healthy individuals. Using this epitope, 92% sensitivity and 100% specificity were reached for IgG detection in Covid-19 samples, and no cross-reactivity with common cold coronaviruses was detected. Likewise, IgM immunoreactivity in samples collected within the first month after symptoms onset showed discrimination ability. Overall, epitope 155–171 from N protein represents a promising candidate for further development and rapid implementation in serological tests.

Publications

Musicò A. et al. Vaccines 2021. https://doi.org/10.3390/vaccines9010035

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

InfImpact. Impact of Full Vaccination with mRNA BNT162b2 on SARS-CoV-2 virus carriage

- Project Coordinator: DITM
- P.I. Elena Pomari
- Other institutions involved: Istituto Zooprofilattico Sperimentale delle Venezie, Legnaro, Italy.
- Start date: 2021
- End date: 2021

Background and purpose

Vaccination reduces the risk of severe disease; however, little is known about virus carriage (including non-sterilising immunity). Thus, studies are required to provide evidence regarding the reduction in transmission by asymptomatic vaccinated individuals that are laboratory-confirmed as SARS-CoV-2-positive.

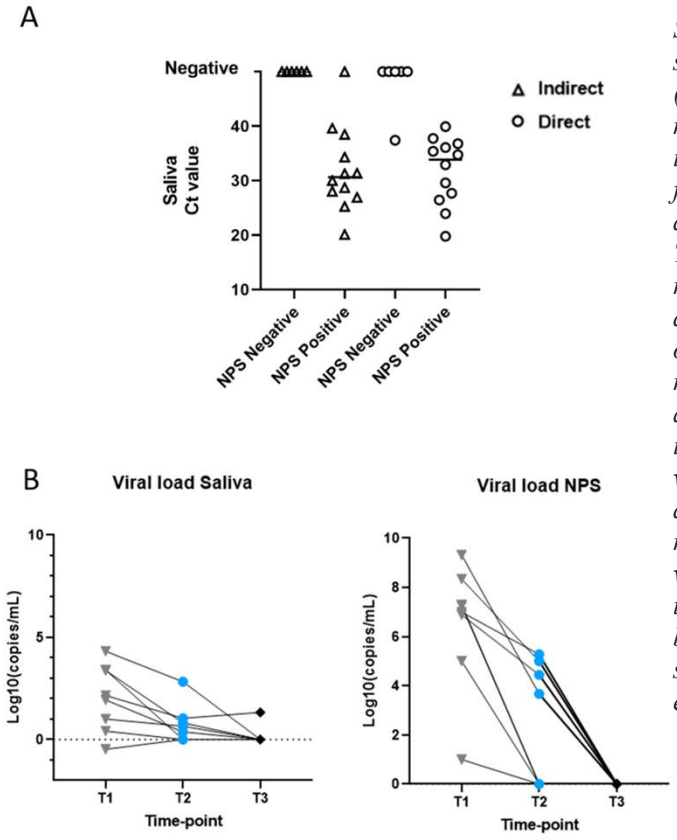
Methods

SARS-CoV-2 infection was monitored in 1898 health care workers (HCWs) after receiving full vaccination with BNT162b2. Consenting individuals found infected provided paired NPS and saliva during the course of infection. Genomic and subgenomic viral

RNAs were investigated using real-time RT-PCR in both biological specimens. The temporal profile of viral load was measured using ddPCR. Viral mutations were also analysed.

Results

Until 30 June 2021, 10 HCWs tested positive for SARS-CoV-2 using real time RT-PCR, resulting in a 4-month cumulative incidence of 0.005%. 8 consenting individuals provided paired NPS and saliva during the course of infection. Subgenomic viral RNA was detected in 8/8 (100%) NPS and in 6/8 (75%) saliva specimens at the baseline. Concordance was observed between NPS and saliva in the detection of viral mutations. Overall, our findings report a low frequency of infected HCWs after full vaccination. It is, therefore, important to monitor the vaccinees in order to identify asymptomatic infected individuals. Saliva can be a surrogate for SARS-CoV-2 surveillance.



SARS-CoV-2 genomic RNA detection in saliva and NPS of 8 health care workers (HCWs) resulted positive after full vaccination. Dots represent data obtained from individual subjects (HCW n. 1–8) at the following time points: T1, 1–2 days after diagnosis; T2, 7–10 days after diagnosis; T3, 10–15 days after diagnosis. (A) Ct results of RT-PCR in saliva by indirect and direct approaches vs. NPS tested positive or negative for SARS-CoV-2 infection. For representation purposes, the undetected amplification of negative results in saliva is reported with Ct > 40. (B) Analysis of viral load variation during infection using ddPCR in NPS and saliva. Each line corresponds to individual HCWs' viral load variation. Gray triangles correspond to the viral load at T1, blue dots to T2, and black rhombuses to T3. Data are represented as Log10copies/mL. For undetected viral load, value is reported equal to 0.

Publications

Deiana M. et al. Microorganisms 2021. https://doi.org/10.3390/microorganisms9081738

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

CovidIgM. Different decay of antibody response and VOC sensitivity in naïve and previously infected subjects at 15 weeks following vaccination

- Project Coordinator: DITM and University of Verona, Italy.
- DITM P.I. Chiara Piubelli
- Other institutions involved: IRCCS San Raffaele, Milan, Italy. Universities of Kent and Greenwich, UK.
- Start date: 2021
- End date: ongoing

Background and purpose

Currently, evaluation of the IgG antibodies specific for the SARS-CoV-2 Spike protein following vaccination is used worldwide to estimate vaccine response. Limited data are available on vaccine-elicited IgM antibodies and their potential implication in immunity to SARS-CoV-2. We aimed at assessing both IgG and IgM response to SARS-cOv-2 vaccination.

Methods

We performed a longitudinal study to quantify anti-S SARS-CoV-2 IgG and IgM (IgG-S and IgM-S) in health care worker (HCW) recipients of the BNT162b2 vaccine. Samples were collected before administration (T0), at the second dose (T1) and three weeks after T1 (T2). The cohort included 1584 immunologically naïve to SARS-CoV-2 (IN) and 289 with history of previous infection (PI).

Results

IN showed three patterns of responses: (a) IgG positive/IgM negative (36.1%), (b) coordinated IgM-S/IgG-S responses appearing at T1 (37.4%) and (c) IgM appearing after IgG (26.3%). Coordinated IgM-S/IgG-S responses were associated with higher IgG titres. IgM-S positive sera had higher pseudovirus neutralization titres compared to the IgM-S negative. Coordinated expression of IgG-S and IgM-S after vaccination

was associated with a significantly more efficient response in both antibody levels and virus-neutralizing activity. The unconventional IgG-S positive/IgM-S negative responses may suggest a recruitment of cross coronaviruses immunity by vaccination, warranting further investigation.

Publications

Ruggiero A. et al. eBioMedicine 2022. https://doi.org/10.1016/j.ebiom.2022.103888

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

ACoRE. Accurate SARS-CoV-2 genome reconstruction for the characterization of intra-host and inter-host viral diversity in clinical samples and for the evaluation of re-infections

- Project Coordinator: University of Verona, Italy.
- DITM P.I. Chiara Piubelli
- Start date: 2020
- End date: 2021

Background and purpose

Sequencing the SARS-CoV-2 genome from clinical samples can be challenging, especially in specimens with low viral titer. Here we report Accurate SARS-CoV-2 genome Reconstruction (ACoRE), an amplicon-based viral genome sequencing workflow for the complete and accurate reconstruction of SARS-CoV-2 sequences from clinical samples, including suboptimal ones that would usually be excluded even if unique and irreplaceable.

Methods

The protocol was optimized to improve flexibility and the combination of technical replicates was established as the central strategy to achieve accurate analysis of low-titer/suboptimal samples.

Results

We achieved complete genome reconstruction and the identification of false-positive variants in >170 clinical samples, thus avoiding the generation of inaccurate and/or incomplete sequences. Most importantly, ACoRE was crucial to identify the correct viral strain responsible of a relapse case, that would be otherwise mis-classified as a re-infection due to missing or incorrect variant identification by a standard workflow.

Publications

Marcolungo L. et al, Genomics, 2021. https://doi.org/10.1016/j.ygeno.2021.04.008

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

COVIDmiRNA. Circulating miRNA in COVID-19

- Project Coordinator: University of Padova, Italy.
- DITM P.I. Chiara Piubelli
- Start date: 2020
- End date: 2021

Background and purpose

SARS-CoV-2 induces a spectrum of clinical conditions ranging from asymptomatic infection to life threatening severe disease. Host microRNAs have been involved in the cytokine storm driven by SARS-CoV-2 infection and proposed as candidate biomarkers for COVID-19.

Methods

To discover signatures of circulating miRNAs associated with COVID-19, disease severity and mortality, small RNA-sequencing was performed on serum samples collected from 89 COVID-19 patients (34 severe, 29 moderate, 26 mild) at hospital admission and from 45 healthy controls (HC). To search for possible sources of miRNAs, investigation of differentially expressed (DE) miRNAs in relevant human cell types *in vitro*.

Results

COVID-19 patients showed upregulation of miRNAs associated with lung disease, vascular damage and inflammation and downregulation of miRNAs that inhibit pro-inflammatory cyto and chemokines, angiogenesis, and stress response. Patients with severe COVID-19 had a miRNA signature indicating a profound impairment of innate and adaptive immune responses, inflammation, lung fibrosis and heart failure. A combination of high serum miR-22-3p and miR-21-5p, targeting antiviral response genes, and low miR-224-5p and miR-155-5p, targeting pro-inflammatory factors, discriminated severe from mild/moderate COVID-19, while low levels of miR-1-3p, miR-23b-3p, miR-141-3p, miR-155-5p and miR-4433b-5p predicted mortality with high sensitivity and specificity.

Publications

Giannella A. et al, Frontiers in immunology, 2022. https://doi.org/10.3389/fimmu.2022.968991

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

Ag_PCR. SARS-CoV-2 rapid antigen test in comparison to RT-PCR

- Project Coordinator: DITM
- P.I. Francesca Perandin
- Start date: 2021
- End date: 2022

Background and purpose

Identification of people infected with severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) is an essential prerequisite for controlling the pandemic spreading. Reverse transcriptase polymerase chain reaction (RT PCR) molecular represents the gold standard for the diagnosis of viral infection, it is very sensitive and accurate and remains the reference method for diagnosing coronavirus disease 2019. However, nucleotide based testing of viral RNA is expensive time consuming, and required specialized laboratory settings, in terms of per-

sonnel and instrumentation. Coronavirus rapid antigen detection (RAD) tests, with the appropriate application in the context of the pandemic, may contribute to the overall diagnostic capacity, offering benefits in terms of response times, and costs for the healthcare system, especially in situations in which the possibility of performing a molecular test on nasopharyngeal swab could be limited.

Methods

We assessed the performance of the Panbio rapid antigen detection (RAD) test for the detection of severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) infection and we compared it with the routine reverse transcriptase polymerase chain reaction (RT PCR) based molecular test in a population of 4167 unselected patients admitted to IRCCS Sacro Cuore Don Calabria Hospital.

Results

Analysis stratified by cycling threshold (C_t) value of SARS CoV 2 gene targets indicated that antigen (Ag) positive C_t values were significantly lower compared to Ag negative values ($p < 0.0001$). Overall, we found discordance in 140, tested negative by RAD and positive by RT PCR, and in 4 resulted positive by RAD and negative by RT PCR. RAD test achieved a sensitivity and specificity of 66.82% and 99.89%, respectively. The positive predictive value was 97.87% while the negative predictive value was 97.62%. The RAD test showed a reliable diagnostic response in subjects that displayed high viral load, while low ability was displayed to identify positive cases with medium low viral load.

Publications

Treggiari D. et al, Journ of Medical Virology, 2021. https://doi.org/10.1002/jmv.27378

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

FluCOVID. Influenza virus during SARS-CoV-2 pandemic

- Project Coordinator: DITM
- P.I. Francesca Perandin
- Start date: 2021
- End date: 2022

Background and purpose

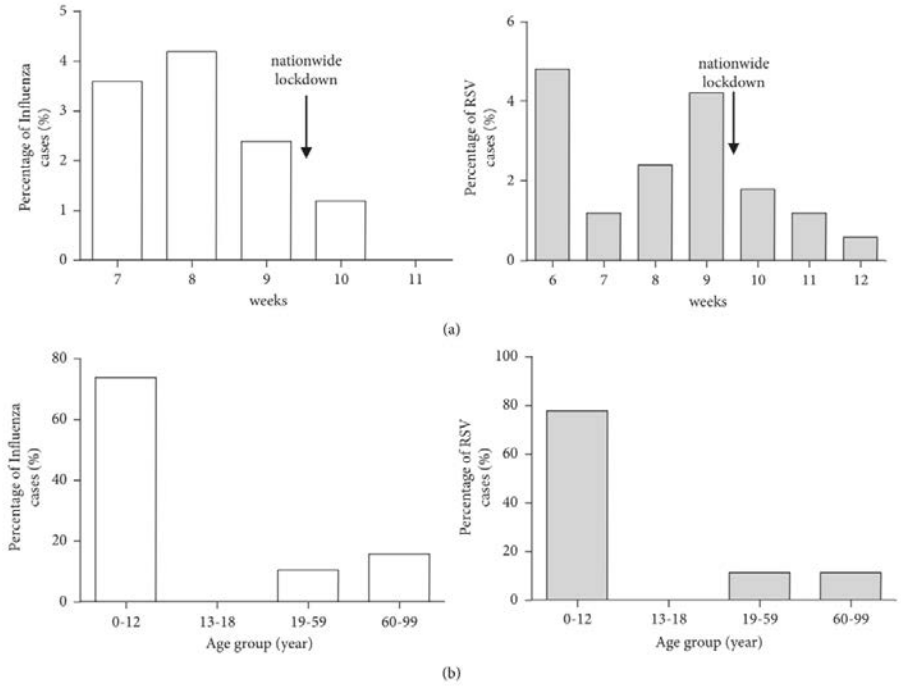
The SARS-CoV-2 virus spread in the Northern Hemisphere during the 2019/2020 influenza seasons and it persisted in the 2021/2022 season. A cocirculation of SARS-CoV-2 and influenza viruses was expected in Italy during the winter seasons. This study aims to investigate the prevalence of influenza and respiratory syncytial viruses observed in a hospital in Verona Province, Italy hospital during these past three winter seasons and to compare our data with national and global surveillance reports on the transmission of respiratory viruses in the preceding decade.

Methods

We performed a retrospective observational analysis of INF-A/B and RSV-A/B molecular diagnostic test results obtained from patients who were referred to IRCCS Sacro Cuore Don Calabria Hospital (Italy). Nasopharyngeal swab samples processed by the routine diagnostics were collected during the seasons 2019/2020 (from week 46 in 2019 to week 12 in 2020), 2020/2021 (from week 47 in 2020 to week 17 in 2021) and 2021/2022 (from week 42 in 2021 to week 4 in 2022).

Results

Our findings clearly demonstrated the extremely low prevalence of influenza virus among hospitalized patients and outpatients during the first two COVID-19 winter seasons, with a reemergence of respiratory syncytial virus in the late 2021. Containment measures may have played an important role in temporarily stopping the circulation of respiratory viruses, but after relaxation, in 2021, we experienced an unusual increase of respiratory syncytial viruses at the beginning of the winter season.



(a) Laboratory-detected cases of influenza A/B and RSV during the 2019-2020 season at our center. Vertical bars show percentage of INF-A/B and RSV positive speciments identified by week 6-7/2020 to 11/12/2020

(b) Distribution of INF-A/B and RSV cases during 2019/2020 season according to age groups.

Publications

Treggiari D. et al, International J Microb, 2022. https://doi.org/10.1155/2022/4915678

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

Research Line n. 2: Neglected Infectious and Tropical Diseases

Line description

The purpose of the research line n. 2 is the study of neglected tropical diseases (NTD) on vulnerable populations in endemic tropical areas, on migrants and on international travelers. The main study objects are focused on the epidemiology, on the search for improved diagnostic markers, as well as the best clinical management

approaches, according to the endemic or non-endemic application contexts. Several activities are conducted as WHO collaborating centre on strongyloidosis and other NTDs and in national (e.g. SIMET, Società Italiana di Medicina Tropicale e Salute Globale) and international networks (e.g. TropNet: the largest European Tropical and Travel Medicine Network). Moreover our centre is collaborating with different limited resources Countries in Africa and South America. The objectives of the research line are: i) the evaluation of the NTD burden in endemic and non-endemic Countries, ii) the development of screening and management protocols for imported cases, iii) the improvement of the diagnostic and prognostic tools for endemic and non-endemic areas, vi) the evaluation of new aspects of the pathophysiology of the disease and of the host-pathogen interaction.

The research line n.2 is organized in different macro-projects, covering clinical/epidemiological and biological aspects of different NTD and other rare diseases:

1. Neglected infections, vulnerable populations (Reference person: Dora Buonfrate).

1. Unravelling the pathophysiology bases and developing of new diagnostic approaches for neglected tropical diseases (Reference person: Chiara Piubelli).

The main disease areas covered by the research projects are strogyloidiasis, filariasis, Chagas disease, schistosomiasis, echinococcosis, leishmaniosis, cysticercosis, histoplasmosis and fungal infections. Other rare diseases infectious diseases according to the Italian Ministry of Health definition are also studied: Whipple Disease and leprosy

A detailed description of the obtained results from the different projects related to Research Line n.2 is reported below, divided by main disease areas.

Macro-project 1: Neglected infections, vulnerable populations

a) Projects focused on the study of NTDs in endemic countries

STH_Glob. The global progress of soil-transmitted helminthiases control in 2020 and World Health Organization targets for 2030

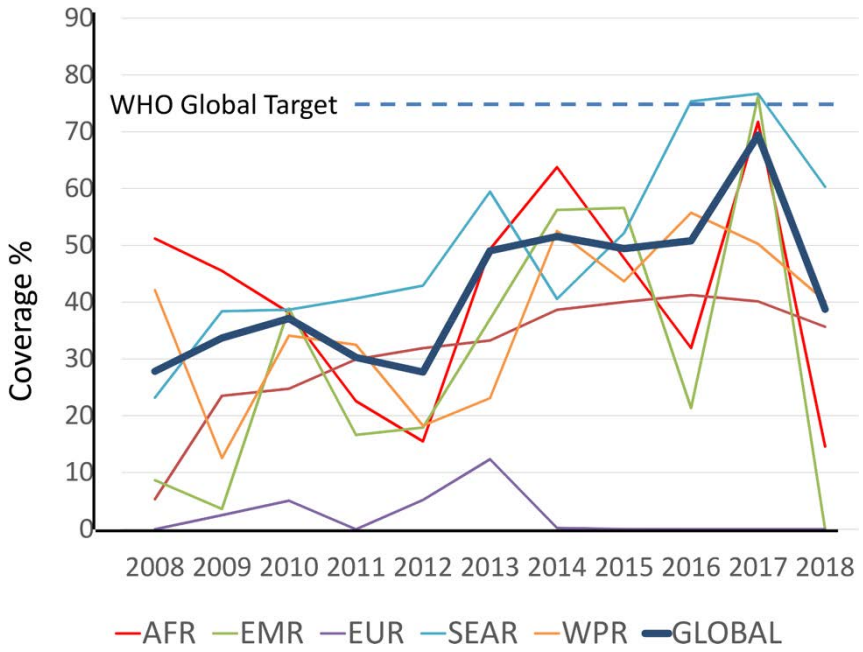
- Project coordinator: WHO-NTD
- DITM P.I.: Dora Buonfrate
- Other institutions involved: WHO Regional Offices. WHO-Collaborating Centres on NTD.

Background and purpose

Soil-transmitted helminth (STH) infections are the most widespread of the neglected tropical diseases, primarily affecting marginalized populations in low- and middle-income countries. More than one billion people are currently infected with STHs. For the control of these infections, the World Health Organization (WHO) recommends an integrated approach, which includes access to appropriate sanitation, hygiene education, and preventive chemotherapy (i.e., large-scale, periodic distribution of anthelmintic drugs). Since 2010, WHO has coordinated two large donations of benzimidazoles to endemic countries, resulting in an important reduction in STH-attributable morbidity in children, while additional tablets have been distributed for the control of lymphatic filariasis.

Methods

This paper (i) summarizes the progress of global STH control between 2008 to 2018 (based on over 690 reports submitted by endemic countries to WHO); (ii) provides regional and country details on preventive chemotherapy coverage; and (iii) indicates the targets identified by WHO for the next decade and the tools that should be developed to attain these targets. Ess of global STH control between 2008 to 2018 (based on over 690 reports submitted by endemic countries to WHO); (ii) provides regional and country details on preventive chemotherapy coverage; and (iii) indicates the targets identified by WHO for the next decade and the tools that should be developed to attain these targets.



Trends in Preventive Chemotherapy coverage in preschool-age children for STH between 2008 and 2018, by WHO region. Data are presented globally and stratified by WHO region (AFR = African Region; AMR = Region of the Americas; EMR = Eastern Mediterranean Region; EUR European Region; SEAR = South East Asian Region; WPR Western Pacific Region).

Conclusions: STH-attributable morbidity can be averted with evidence-informed program planning, implementation, and monitoring. Caution will still need to be exercised in stopping control programs to avoid any rebound of prevalence and loss of accrued morbidity gains. Over the next decade, with increased country leadership and multi-sector engagement, the goal of eliminating STH infections as a public health problem can be achieved.

Publications

Montresor A. et al, PLOS Negl Trop Dis., 2020. https ://doi.org/10.1371/journal.pntd.0008505

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

EchinTanz. Cystic echinococcosis in northern Tanzania

- Project coordinator: DITM

- P.I.: Francesca Tamarozzi
- Other institutions involved: Kilimanjaro Clinical Research Institute, Moshi, Tanzania. Kilimanjaro Christian Medical University College, Moshi, Tanzania. University of Glasgow, UK. Istituto Superiore di Sanità, Rome, Italy.

Background and purpose

There are close similarities between the life-cycles of Echinococcus granulosus sensu lato (E. granulosus s.l.) that causes cystic echinococcosis (CE) in humans and Taenia multiceps/Coenurus cerebralis that causes cerebral coenurosis in small ruminants. Recent evidence highlights that livestock in Maasai communities of northern Tanzania are suffering from increases in the prevalence of cerebral coenurosis, leading to concerns about a possible concurrent increased risk of human CE. The aim of this study was to estimate the prevalence of human abdominal CE and the prevalence and species/genotypes of E. granulosus s.l. in livestock in Maasai communities.

Methods

Human CE was diagnosed by abdominal ultrasound on volunteers aged ≥ 7 years in five villages in the Longido and Ngorongoro Districts in northern Tanzania. Infection in ruminants was evaluated through inspection in local abattoirs, followed by molecular identification of one cyst per animal, with a priority for hepatic cysts, using PCR targeting of the cytochrome c oxidase I gene (COX1), followed by restriction fragment length polymorphism and multiplex PCR, and sequencing of non-E. granulosus s.l. samples.

Results

Ultrasound was performed on 823 volunteers. Hepatic CE cases were diagnosed only in Ngorongoro (n = 6; 1.3%), of which three had active cysts. Village-level prevalence of CE ranged between 0 and 2.4%. Of the 697 ruminants inspected, 34.4% had parasitic cysts. Multiple species/genotypes of E. granulosus s.l. are circulating in Maasai communities of northern Tanzania. More precise estimation of the prevalence in this area and a better understanding of the specific risk factors for CE is needed. Interventions targeting transmission routes common to both E. granulosus s.l. and T. multiceps would have dual benefits for preventing both human and livestock disease.

Publications

Tamarozzi F. et al, Parasites & Vectors, 2022. https://doi.org/10.1186/s13071-022-05518-x

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Research Grant 2019

European Union Horizon 2020 Research and Innovation Programme grant agreement N773830: One Health European Joint Programme, Project "MEME"

OnchoEpilepsy. Potential Parasitic Causes of Epilepsy in an Onchocerciasis Endemic Area

- Project coordinator: University of Antwerp, Belgium.
- Other institutions involved: Division Provincial de la Santé, Ituri, Bunia, Democratic Republic of Congo
- Start date: 2019
- End date: 2021

Background and purpose

A high burden of epilepsy is observed in Africa where parasitological infections are endemic. In 2016, in an Onchocerciasis endemic area in the Logo health zone, in Ituri province in the Democratic Republic of Congo, a door-to-door study showed an epilepsy prevalence of 4.6%, and 50.6% of persons with epilepsy were infected with *Onchocerca volvulus*.

Methods

In the current study, the serum of 195 people infected with *O. volvulus* persons with epilepsy were tested to determine the proportion of co-infections with *Taenia solium, Toxocara canis* and *Strongyloides*.

Results

These proportions were, respectively, 8.2, 18.5 and 12.8%. Persons with a *T. solium* co-infection were older than those without co-infection ($p = 0.021$). In six (37.5%) of the *T. solium* co-infected persons, the first seizures appeared after the age of 30 years compared to three (2.1%) persons without a co-infection ($p < 0.0001$). Our study suggests that an *O. volvulus* infection is the main parasitic cause of epilepsy in the Ituri province, but in some persons, mainly in those with late onset epilepsy and with

focal seizures, the epilepsy may be caused by neurocysticercosis. As the population in the area rears pigs, activities to limit *T. solium* transmission should be implemented.

Publications

Vieri MK et al, pathogens, 2021. https://doi.org/10.3390/pathogens10030359

Funding

European Research Council (ERC 671055)
VLIRUOS (Flemish Interuniversity Council for University Development Cooperation)
Fondo Ricerca Corrente, Italian Ministry of Health.

b) Projects focused on the study of NTDs in Europe, in the COVID-19 era

NTD_COVID. Neglected tropical diseases in non-endemic countries in the era of COVID-19 pandemic: the great forgotten

- Project coordinator: University of Florence, Italy
- Other institutions involved: Oxford University, UK.
- DITM P.I. Federico Gobbi
- Start date: 2020
- End date: 2021

In non-endemic countries, the access to healthcare for migrants and other patients with NTDs may be hampered by new barriers linked to the COVID-19 pandemic. Low awareness of health care professionals on the opportunistic potential of some NTDs may lead to unfavorable outcome of COVID-19 patients treated with immunomodulatory drugs.

Publications

Tilli M. et al, Journal of Travel Medicine, 2020. https://doi.org/10.1093/jtm/taaa179

EchinEuro. Epidemiological distribution of Echinococcus granulosus s.l. infection in human and domestic animal hosts in Europe

- Project coordinator: DITM
- P.I.: Francesca Tamarozzi
- Other institutions involved: Department of Animal Medicine, Production and Health, University of Padova, Legnaro (Padova), Italy.

Background and purpose

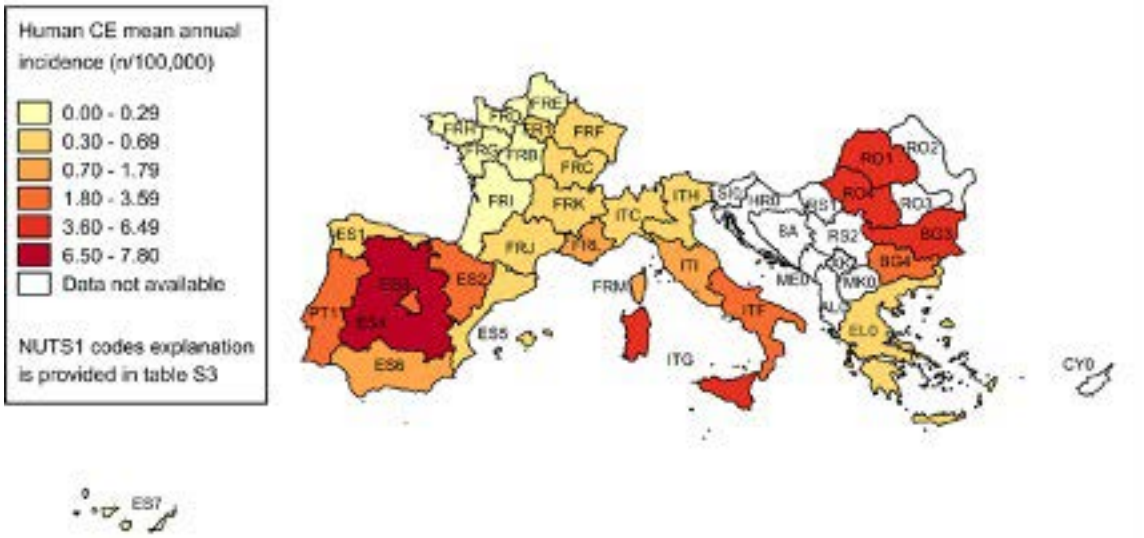
Cystic echinococcosis (CE) is a neglected zoonosis caused by infection with the cestode Echinococcus granulosus sensu lato.

Methods

We carried out a systematic literature review on E. granulosus s.l. human and animal (cattle, sheep, dog) infection in European Mediterranean and Balkan countries in 2000-2019, to provide a picture of its recent epidemiology in this endemic area. MEDLINE, EMBASE, Scopus, Google Scholar and Open Grey databases were searched. Included cases were: i) for humans, data from hospital records and imaging studies; ii) for dogs, data from necropsy and coprological studies; iii) for ruminants, cases based on slaughter inspection. Data were extracted from 79 publications, 25 on human infection (covering 437 epidemiological units), and 54 on animal infection (52 epidemiological units for cattle, 35 for sheep and 25 for dogs).

Results

Average annual incidence rates of human CE ranged from 0.10-7.74/100,000; pooled prevalence values ranged from 0.003-64.09% in cattle, 0.004-68.73% in sheep, and 0-31.86% in dogs. Southern and insular Italy, central Spain, Romania and Bulgaria reported the highest values. Limitation of evidence included the paucity of human prevalence studies, data heterogeneity, and the patchy geographical coverage. Our results confirm Italy, Spain, and Eastern Europe being the most affected areas. Results also highlight the notorious problem of underreporting of E. granulosus s.l. infection in both humans and animals.



Spatial distribution of average human incidence rates. Average incidence values at NUTS1 level are visualised with progressively intense colours according to ranges established by Jenks optimization method and manually adjusted for a better results visualisation. Data at country level are reported only if more detailed data at NUTS1 level were not available (source of NUTS shapefiles: Eurostat).

Publications

Tamarozzi F. et al, PLOS Negl Trop Dis, 2020. https://doi.org/10.1371/journal.pntd.0008519

Funding

Grant (BIRD174940) by the Department of Animal Medicine, Production and Health of the University of Padova

EchinBurden. A One-Health evaluation of the burden of cystic echinococcosis and its prevention costs

- Project coordinator: Department of Animal Medicine, Production and Health, University of Padova, Legnaro (Padova), Italy.
- DITM P.I.: Francesca Tamarozzi
- Other institutions involved: University of Bologna, Veneto Region, Azienda ULSS 9 Scaligera, Verona, Italy, Istituto Superiore di Sanità, Roma, Italy.

Background and purpose

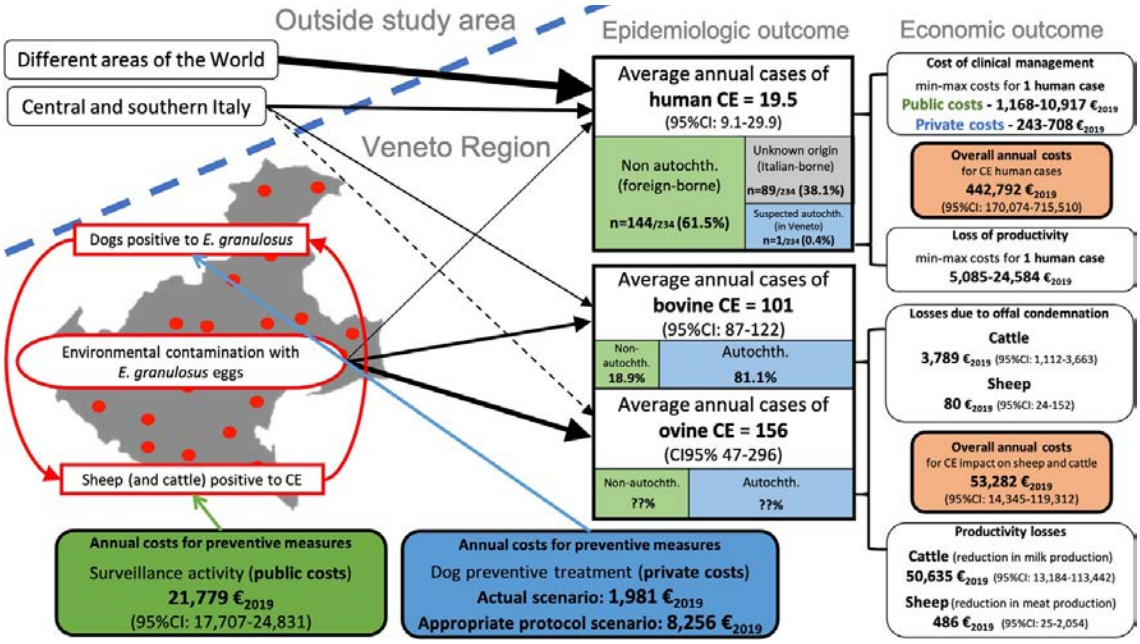
An integrated model, based on a One Health approach, was implemented to estimate the epidemiological and economic outcomes of cystic echinococcosis (CE) in Veneto region, an hypo-endemic area of Northern Italy, and the costs for its prevention.

Methods

Data and information needed to populate the model were retrieved from published literature, official statistics, expert opinions, or actively searched through data mining (i.e., Hospital and slaughterhouse data), when fundamental data were not available. Human-health and animal-health costs, both public and private, were considered.

Results

The overall impact of CE in the study area was estimated in an yearly cost of about 0.5 million €, due to an average of 19.5 human hospitalized cases and about 200 infected animals among cattle and sheep, per year. The human:animal costs ratio was about 8:1. Most of the infected animals were autochthonous. No specific action resulted to be in place for human surveillance, while veterinary surveillance accounted for a yearly cost of about 22,000 €. The source of most of the human cases was likely external to the study area, and their economic impact accounts for a cost that is far exceeding that of surveillance and preventive actions in place in the veterinary sector.



Flow chart reporting the main epidemiological and economic outcomes of CE in the Veneto region, on an annual basis

Publications

Cassini R. et al, One Health, 2021. https://doi.org/10.1016/j.onehlt.2021.100320

Funding

Project "Evaluation of policy measures to control two emerging parasitic diseases (Cystic Echinococcosis and Leishmaniasis) in Veneto Region using a One Health approach" (cod. BIRD174940), granted in the framework of the Departmental integrated research budget of the University of Padova, year 2017.

EurSchisto. Autochthonous schistosomiasis in Europe: A silent threat

- Project coordinator: Hospital Universitario La Paz-Carlos III, Madrid, Spain
- DITM P.I. Federico Gobbi
- Start date: 2021
- End date: 2022

Background and purpose

Autochthonous schistosomiasis in Europe was previously described in Corsica and in other sites. A new report from Almeria, Spain, adds the fourth well documented focus of autochthonous transmission in Europe.

Methods

Herein, we review the reports of autochthonous schistosomiasis in Europe, starting with the first report from Portugal in 1920.

Results

It was not until 2013 when the following outbreak was reported involving more than 100 people in Corsica Island (Cavu river) by an hybrid of S. hematobium and S. bovis, that is still ongoing. Recently, other local cases have been described in Corsica (Solenzana river). Investigations conducted in Corsica and Spain to detect the parasite in snails resulted negative. The intensification of human activities, the increase of migration from endemic countries, the adaption of Schistosoma spp. to overwinter and the fact that the adult worm can parasitize the host for periods of up to 40 years, may lead to the emergence of local schistosomiasis, especially in southern Europe.

Publications

Arsuaga M. et al, Travel Med and Inf Dis, 2022. https://doi.org/10.1016/j.tmaid.2021.102244

Results

Fondo Ricerca Corrente, Italian Ministry of Health.

c) Projects focused on the study of clinical and epidemiological aspects of Strongyloides stercoralis infection

IverNeed. Estimate of global prevalence of strongyloidiasis and of ivermectin drug needs for strongyloidiasis

- Project coordinator: DITM
- P.I.: Dora Buonfrate
- Other institutions involved: OMS, NTD Department (dr Montresor); RTI International (Dr Bisanzio)

Background and purpose

Currently, no specific strategies have been implemented at global level for the control of *S. stercoralis* infection. The PC programmes targeting the other STH rely on different drugs, that have low efficacy against *S. stercoralis*, hence we cannot expect them to significantly reduce the prevalence of strongyloidiasis. On the other hand, the use of ivermectin in preventive chemotherapy (PC) programmes for the eradication of lymphatic filariasis and onchocercosis showed an indirect impact on the prevalence of strongyloidiasis, that dramatically declined in the areas targeted, and was maintained at low levels even years after the cessation of the programmes. Moreover, there is evidence on the good tolerability and efficacy of PC with a combination of albendazole and IVM, as it has been confirmed by a recent systematic review with meta-analysis. Therefore, integrating PC programmes for STH with ivermectin seems a reasonable approach, that would also benefit of the already-existing infrastructure, reducing the costs for the implementation of an *ex-novo* control programme.

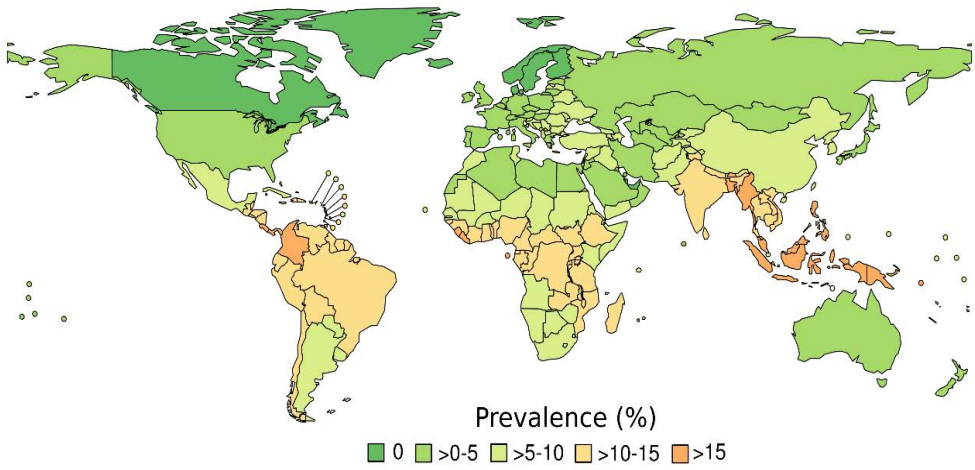
Objective of this study is to estimate the amount of ivermectin needed for the implementation of a possible global control program for *S. stercoralis* based on preventive chemotherapy.

Methods

Update of a review of literature on the global prevalence of strongyloidiasis. In case of strongyloidiasis, the sensitivity of the different diagnostic methods available is very different and this do not allow a direct comparison of the results from studies conducted with different diagnostic. For this reason, a conversion table (with statistical adjustment based on the diagnostic tests used) allowing to appraisal the "real" prevalence from the one estimated by the original study will be produced. This table will be based on data retrieved from studies comparing sensitivity of the different diagnostic methods. This conversion table will allow to adjust the original prevalence results in each country and to make them comparable. Model to extend the estimates of prevalence to areas where there is no information: identification of possible relevant predictors and evaluation of their relevance by regression methodology (climatic predictors, population density predictors, sanitation). If enough data will be retrieved, a Global strongyloidiasis map will be created.

Results

We estimate the global prevalence of strongyloidiasis in 2017 to be 8.1% (95% CI: 4.2–12.4%), corresponding to 613.9 (95% CI: 313.1–910.1) million people infected. The South-East Asia, African, and Western Pacific Regions accounted for 76.1% of the global infections. Our results could be used to identify those countries in which strongyloidiasis prevalence is highest and where mass drug administration (MDA) should be deployed for its prevention and control.



Estimated strongyloidiasis prevalence (STG-PR) or 2017, as predicted by the best statistical model.

Publications

Buonfrate D. et al, Pathogens, 2020. https://doi.org/10.3390/pathogens9060468

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

EcuStrong. Strongyloides stercoralis mapping in Ecuador

- Project coordinator: DITM
- P.I. Dora Buonfrate
- Start date: 2019
- End date: 2020
- Other institutions involved: Universidad Central de Quito, Ecuador; CECOMET Esmeraldas, Ecuador.

Background and purpose

Data on the prevalence of strongyloidiasis in Ecuador are patchy. The aim of this study was to document the presence of *Strongyloides stercoralis* infection in rural communities of different provinces of Ecuador.

Methods

We tested 1,418 serum samples stored at the biobank of the Central University of Ecuador, Quito, with an ELISA test for *Strongyloides*. The samples had been collected in eight different provinces of Ecuador.

Results

Two hundred ninety-four samples (20.7%) were positive, and Jipijapa, Manabí Province, was the site with the largest proportion of positive samples (66.7%). Further surveys aimed at estimating the prevalence of the infection should be carried out in areas where the infection seems highly prevalent, and ad hoc control measures should be adopted.

Publications

Guevara AC et al, Am J Trop Med & Hygiene, 2020. https://doi.org/10.4269/ajtmh.19-0565

IverSafe. Safety of higher doses ivermectin.

- Project coordinator: Universidad Miguel Hernández de Elche, Alicante, Spain
- DITM P.I. Dora Buonfrate
- Other institutions involved: ISGlobal Barcelona; CRFMT Yaounde, Cameroon; IRD Miontpellier, France; CONICET, Orán, Argentina.
- Start date: 2019
- End date: 2020

Background and purpose

Ivermectin is a key anthelmintic for the control of neglected tropical diseases. The main indications for population-level control with ivermectin through mass drug administration are onchocerciasis and lymphatic filariasis; however, there is interest in using higher, fixed-dose regimens for the control of scabies, soil-transmitted helminths and malaria. Safety data for these higher-dose regimens are needed.

Methods

A systematic literature review and meta-analysis on the safety and doses of ivermectin was conducted. Eligible studies reported patient-level data and, for the meta-analysis, clinical trials reporting data on doses ≥200 and ≥400 µg/kg were included. Incidence ratios were used to compare adverse events by severity and organ system affected.

Results

The systematic search identified six studies for inclusion, revealing no differences in the number of individuals experiencing adverse events. A descriptive analysis of these clinical trials for a variety of indications showed no difference in the severity of the adverse events between standard (up to 400 µg/kg) and higher doses of ivermectin. Organ system involvement only showed an increase in ocular events in the higher-dose group in one trial.

Publications

Navarro M. et al, J of Antimicrobial Chemoterapy, 2020. https://doi.org/10.1093/jac/dkz524

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

IverMilk. Ivermectin levels in human breastmilk

- Project coordinator: DITM
- P.I. Andrea Angheben
- Start date: 2019
- End date: 2020

Background and purpose

Ivermectin is a widely used drug for the treatment of various neglected tropical diseases, such as lymphatic filariasis, onchocerciasis, and strongyloidiasis among others. Despite its excellent safety profile, there are few published studies of the use of ivermectin in children, pregnant and nursing women. In the present study, we report clinical data on ivermectin concentrations in breastmilk of a woman with *Strongyloides stercoralis* and HTLV-I coinfection.

Methods

Assessment of ivermectin concentration in breastmilk at different intervals after administration of ivermectin single dose of 200 µg/kg

Results

Ivermectin levels in breastmilk ranged from 1.4 to 20.8 ng/ml, with a mean of 9.26 ng/ml after a single dose of 200 µg/kg. We estimated the possible ivermectin exposure of the infant to be 1.1 µg/kg, 0.55% of the weight-adjusted percentage of the maternal dose. This value is largely under the threshold established by the World Health Organization for safe breastfeeding. The findings from this case study do not support exclusion of lactating women or interrupting lactation.

Publications

Rodari P et al. Acta Trop., 2020. doi: https://doi.org/10.1016/j.actatropica.2019.105249

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

StrongClin. A review of the clinical features of S. stercoralis infection

- Project coordinator: DITM
- P.I. Dora Buonfrate
- Other institutions involved: ITM Anrtwerp, Belgium
- Start date: 2020
- End date: 2021

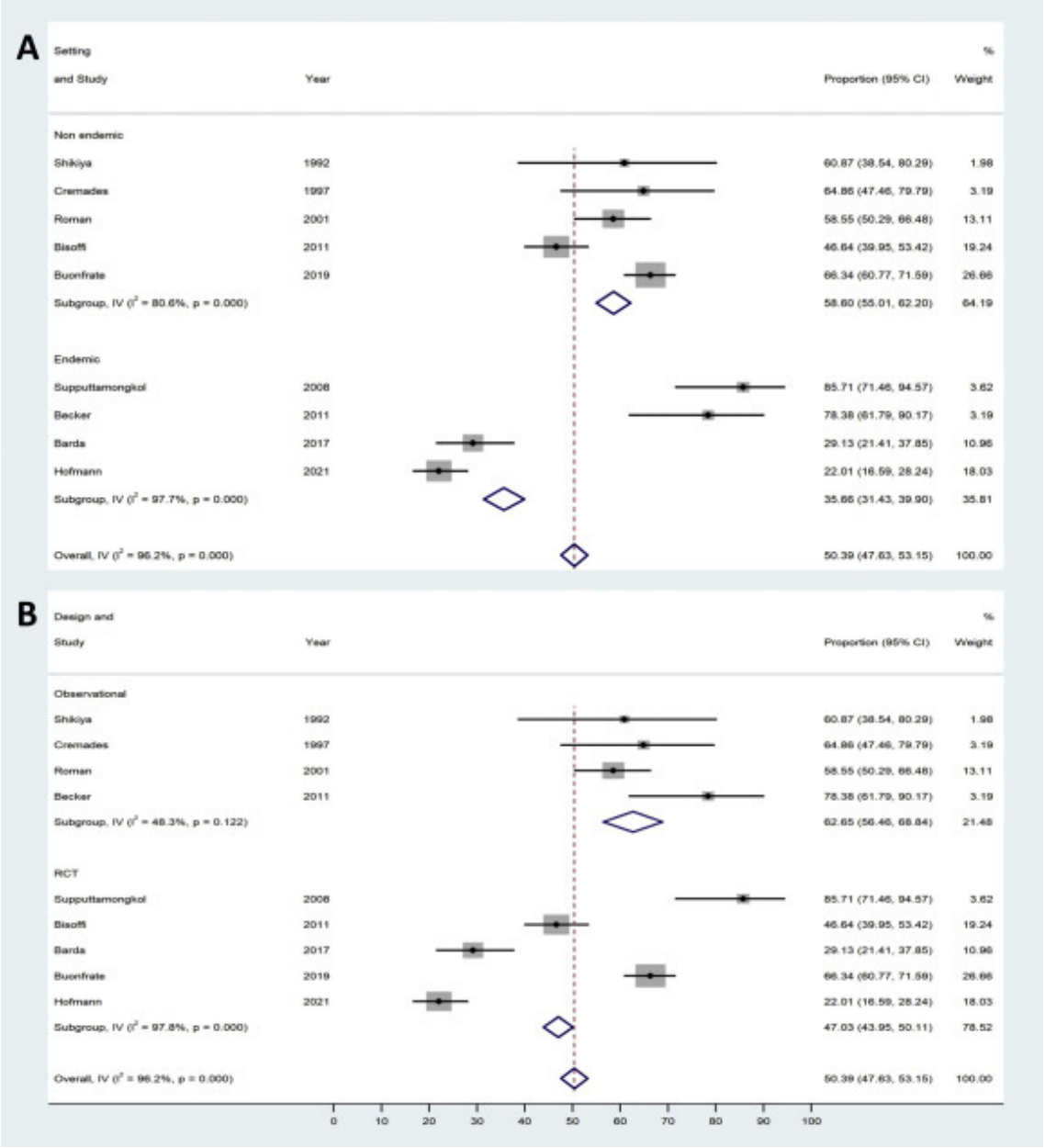
Background and purpose

The clinical and laboratory characterization of *Strongyloides stercoralis* infection at diagnosis and after treatment is still poorly defined.

Objectives: The primary objective was to describe the pattern and frequency of clinical and laboratory characteristics associated with S. stercoralis infection. The secondary objectives were (a) comparison of characteristics reported in endemic versus non-endemic areas; and (b) the evaluation of the resolution of identified characteristics after treatment.

Methods

We searched PubMed, EMBASE, LILACS and CENTRAL up to May 2021. Eligible studies were randomized controlled trials (RCTs) for the treatment of S. stercoralis infection and prospective observational studies reporting data on symptoms caused by strongyloidiasis in individuals diagnosed with a highly specific test. Quality assessment was performed to assess the risk of bias. Demographic and clinical data were summarized using descriptive statistics. Meta-analysis was done by pooling the proportion of participants with symptoms with random effects model.



Propotion of people reporting symptomatic infection. (A) Forest plot showing the frequency of symptomatic infection reported in each study. The diamonds synthetize ovreall frequency (at the bottom of the figure) and for each setting (non-endemic/endemic). (B) Forest plot showing the frequency of symptomatic infection reported in each study. the diamonds synthtize ovreall frequency among studies (at the bottom of the figure) and for study design (observational studies and randomized controlled trials)

Results

Twenty studies were included. Overall, symptoms were reported in 50.4% cases. Frequency of symptoms tended to reduce after treatment. About half of infected

people complain at least of one symptom and almost 70% have eosinophilia. The frequency of symptoms and eosinophilia decreased after treatment. Providing relief from symptoms and eosinophilia is another reason, in addition to prevention of disseminated disease, for promoting screening and treatment of individuals with strongyloidiasis.

Publications

Buonfrate D. et al, Clin. Microb and Infection, 2021. https://doi.org/10.1016/j.cmi.2021.07.016

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

d) Projects focused on the control of strongyloidiasis

StrongDog. Strongyloides stercoralis infection in dogs and risk for humans

- Project coordinator: DITM
- P.I. Dora Buonfrate
- Other institutions involved: University of Bari, Bari, Italy. University of Sydney, Sydney, New South Wales, Australia. University of Florence, Italy Sapienza University of Rome, Italy.
- Start date: 2019
- End date: 2020

Background and purpose

Autochthonous human and canine strongyloidiasis is reported in Europe but is unclear whether the transmission of infection still occurs. Recently, a collaboration between the our IRCCS with the University of Bari showed that cases of S. stercoralis infection in dogs are present in our country, although it could not be proven whether this caused transmission of the infection to humans. Having observed a highly suggestive case, we aimed to describe the case in detail and review the relevant literature.

Methods

a. Case report.

b. Systematic review of the literature on autochthonous human and canine strongylodiasis in Europe to investigate the current dynamic of transmission.

Results

We describe an autochthonous case of strongyloidiasis in an Italian girl. Overall, 109 papers were included in the review and one unpublished Italian case was added. Eighty human case reports were retrieved and 42 had severe strongyloidiasis. Most cases were diagnosed in Spain, Italy and France. Canine strongyloidiasis was reported mainly in Italy (68 cases), but a few cases occurred also in other countries. Further investigations are needed to clarify the zoonotic transmission of this nematode.

Publications

Ottino L. et al, Pathogens, 2020. https://doi.org/10.3390/pathogens9060439

Funding

None

StrongCost. Cost-effectiveness of strongyloidiasis screening strategies in migrants in Italy and Spain

- Project coordinator: DITM jointly with the other institutions involved (see below)
- P.I.s Dora Buonfrate (Italian study) and Ana Requena (Spanish study)
- Other institutions involved: Hospital Universitari San Juan de Alicante, Karolinska Institutet, Stockholm, ISGLOBAL Barcelona, University of Florence, WHO-NTD
- Start date: 2019
- End date: 2021

Background and purpose

Implementation of control programmes for Strongyloides stercoralis infection is among the targets of the World Health Organization Roadmap to 2030. The best strategy for controlling morbidity due to imported strongyloidiasis in migrants is un-

clear.

Methods

Cost-effectiveness assessment.

Results

In the Spanish study, presumptively treating all immunosuppressed migrants from areas with endemic *Strongyloides* would generate cost savings to the health system and was considered the most cost-effective approach. The Italian study yelded partially different results, concluding that, compared to the current practice (passive diagnosis), both screening and presumptive treatment strategies are more favorable from a cost-effectiveness point of view, with a slight advantage of the screening strategy in a one-year time horizon. The partial difference in results is explained, in part, by the differences in methods, and in part by different health costing systems in the two countries.

Publications

Wilkman-Jorgensen PE et al, BMJ Global Health, https://doi.org/10.1136/bmjgh-2020-002321

Zammarchi L. et al, Travel Med & Inf Dis, 2020. https://doi.org/10.1016/j.tmaid.2020.101561

Funding

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Agència de Gestio' d'Ajuts Universitaris I deRecerca (AGAUR)

Tropical Disease Cooperative Research Network

Fondo Ricerca Corrente, Italian Ministry of Health. INMP.

Bando 2016 per finanziamento di progetti competitivi per ricercatori a tempo determinato dell'Università di Firenze

e) The following projects mainly comprises studies carried out on NTD in migrants

Neurocyst. Neurocysticercosis-related seizures in the post-partum period

- Project coordinator: DITM
- P.I. Tamara Ursini
- Start date: 2019
- End date: 2021
- Other institutions involved: IRCCS Istituto Neurologico Carlo Besta, Milan, Italy. University of Florence, Italy. Santa Chiara Hospital, Trento, Italy.

Background and purpose

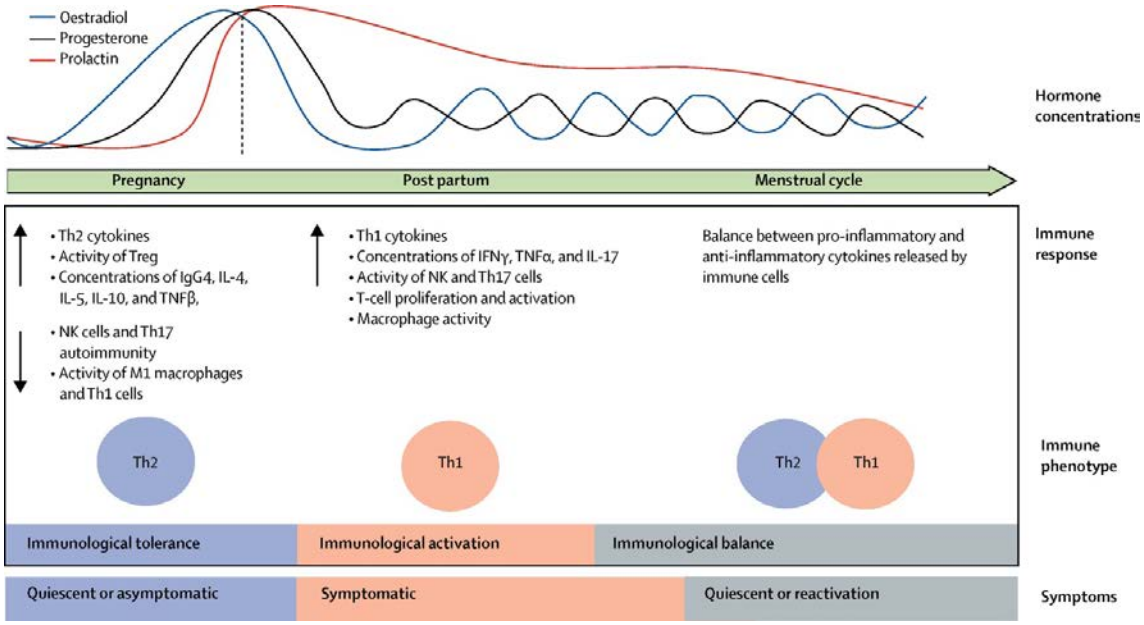
Neurocysticercosis, the infection of the CNS with larval cysts of Taenia solium, is a leading cause of seizures in low-income countries. The clinical presentation of neurocysticercosis is variable and depends on the number, size, and location of cysticerci, and on the immune response of the host. In most patients, the affected site is the brain parenchyma, where cysts can precipitate seizures. Neurocysticercosis has seldom been described in pregnant women. .

Methods

In this Grand Round, we report two cases of pregnant women who immigrated to Italy from Bolivia and Ecuador, and who developed seizures in the early post-partum period, due to calcified parenchymal neurocysticercosis lesions. We discuss the complex interactions between neurocysticercosis and the immune system in pregnancy and the post-partum period.

Results

Building on this scenario, we propose practices for the management of neurocysticercosis in pregnancy and the post-partum period, highlighting important gaps in the literature that should be addressed.



during pregnancy, changes in the concentrations of sex steroids might lead to immunological shifts in the balance between the anti inflammatory and pro inflammatory responses. […] The pro-inflammatory cells' activity reduction, combined with the increased activity of regulatory T cells and production of anti-inflammatory cytokines, contribute substantially to the worse outcomes from infectious diseases seen during pregnancy

Publications

Ursini T. et al, The Lancet Inf Dis, 2020. https://doi.org/10.1016/S1473-3099(20)30240-J

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

DITM_INMP. Neglected Tropical Diseases and migrants. A global challenge

- Project coordinator: DITM
- P.I. Zeno Bisoffi
- Other institutions involved: INMP Rome, Italy.
- Start date: 2018
- End date: Ongoing

Background and purpose

"Neglected" tropical diseases (NTDs) in Europe and in Italy are largely a problem of "Neglected" people, namely, immigrants, refugees and asylum seekers. Preliminary studies carried out retrospectively show that the prevalence of some NTD of major concern is striking and that the vast majority are undiagnosed and thus untreated, despite the existence of specific guidelines.

This project aims to follow a prospective cohort of immigrants submitted at NTD screening at INMP in Rome, with two main purposes:

a. assess the real prevalence of major NTDs targeted by guidelines;

b. improve the diagnosis and management of NTD and other infections in this vulnerable population.

Methods

Prospective prevalence study. Assessment of accuracy of diagnostic tools for screening and diagnosis of selected NTD in immigrants and refugees.

Results

In a particularly vulnerable group, Female Sex Workers from Nigeria, major NTD, strongyloidiasis and schistosomiasis, were much more prevalent than Sexually transmitted Infections (STI), albeit being virtually ignored by the health system. 2. In a large cohort of African refugees and asylum seekers consecutively enrolled for screening purpose, prevalence of *Strongyloides* and schistosoma infection were 8.8% and 31%, respectively. 3. A new ELISA test for screening of strongyloidiasis was evaluated, showing (at Latent Class Analysis, LCA) 91% sensitivity and 88% specificity.

Publications

Buonfrate D. et al, Microorganisms, 2021. https://doi.org/10.3390/microorganisms9020401

Marrone R. et al, Pathogens, 2023. https://doi.org/10.3390/pathogens12020274

Funding

Fondo Ricerca Corrente, Italian Ministry of Health. INMP.

LatinNTD. Prevalence of Chagas disease and strongyloidiasis among HIV-infected Latin American immigrants

- Project coordinator: DITM
- P.I. Paola Rodari
- Other institutions involved: INMI Spallanzani IRCCS Rome, Italy. ICONA Foundation, Milan, Italy. Institute for Global Health UCL, London, UK. ASST Santi Paolo e Carlo, University of Milan, Italy.
- Start date: 2020
- End date: 2022

Background and purpose

Screening HIV-positive migrants for neglected tropical diseases having potential for life-threatening reactivation, such as Chagas disease and strongyloidiasis is not widely implemented. We evaluated the prevalence of these infections among a large cohort of HIV-infected migrants from Latin America living in Italy.

Methods

Cross-sectional study evaluating the prevalence of Trypanosoma cruzi and Strongyloides stercoralis infections in HIV-infected migrants from Latin America enrolled in the Italian Cohort of Antiretroviral-Naïve patients (ICONA) between 1997 and 2018, based on serology performed on sera stored in the ICONA Foundation biobank. Screening for Chagas disease was performed using two commercial ELISA complemented by commercial Immunoblot and CLIA if discordant. Strongyloidiasis

was evaluated using a commercial ELISA.

Results

389 patients were analysed. Fifteen (3.86%) had at least one positive Chagas ELISA test. Prevalence of Chagas disease was 0.5% or 1.29% depending on the confirmatory technique. Serology for strongyloidiasis was positive in 16 (4.11%) patients. Only Nadir CD4+ T cell count was associated with discordant serology for Chagas disease (p = 0.046).

Conclusions: The accuracy of seroassays for Chagas disease and strongyloidiasis in HIV-positive patients is unclear. To avoid missing potentially life-threatening infections, we suggest implementing additional diagnostic strategies in at-risk patients with inconclusive serology results.

Publications

Rodari P. et al, Trav Med & Inf Dis, 2022. https://doi.org/10.1016/j.tmaid.2022.102324

Funding

Fondo Ricerca Corrente, Italian Ministry of Health. INMP.

ChagasMothChild. Ongoing mother-to-child transmission of Chagas disease in Italy

- Project coordinator: University of Florence, Italy.
- DITM P.I. Andrea Angheben
- Other institutions involved: Anna Meyer Children's University Hospital, Florence, Italy. WHO-NTD.
- Start date: 2019
- End date: 2021

Background and purpose

Mother-to-child transmission (MTCT), mostly congenital, is currently the second more common route of transmission for CD worldwide, accounting for 22.5% of the 38 593 incident cases per year in continental Latin America (LA). Outside LA, where the transmission by insect vectors does not occur and screening of blood donors and transplant donors and recipients have been implemented, MTCT is the first route of transmission hampering the elimination of the disease.

Methods

We reviewed reports of MTCT and related policies in non-endemic countries.

Results

According to a review published in 2016, in non-endemic setting, formal health policies on control and management of congenital CD transmission are absent except in three regions (Catalonia, Galicia, and Valencia) in Spain, one region (Tuscany) and one province (Bergamo) in Italy.Ref 3S However, in Spain, and for a less extent other countries such as Italy and Switzerland, some additional spontaneous initiatives of screening for CD in pregnant women exist at local institutional level. In Italy, one case of congenital infection has been reported in a child born from a Bolivian woman in Bergamo. Non-endemic countries and territories should urgently implement these public health measures in order to eliminate CD MTCT

Publications

Zammarchi L. et al, J Trav Med, 2021. https://doi.org/10.1093/jtm/taaa201

Funding

Fondo Ricerca Corrente, Italian Ministry of Health. INMP.

f) Projects focused on filariasis

MansonPer. Mansonella perstans case series

- Project coordinator: DITM
- P.I. Federico Gobbi
- Start date: 2019
- End date: 2022
- Other institutions involved: TropNet. ITM Antwerp, Belgium. Hospital de Poniente, Almería, Spain. Vall d'Hebron University Hospital, Barcelona, Spain.

Background and purpose

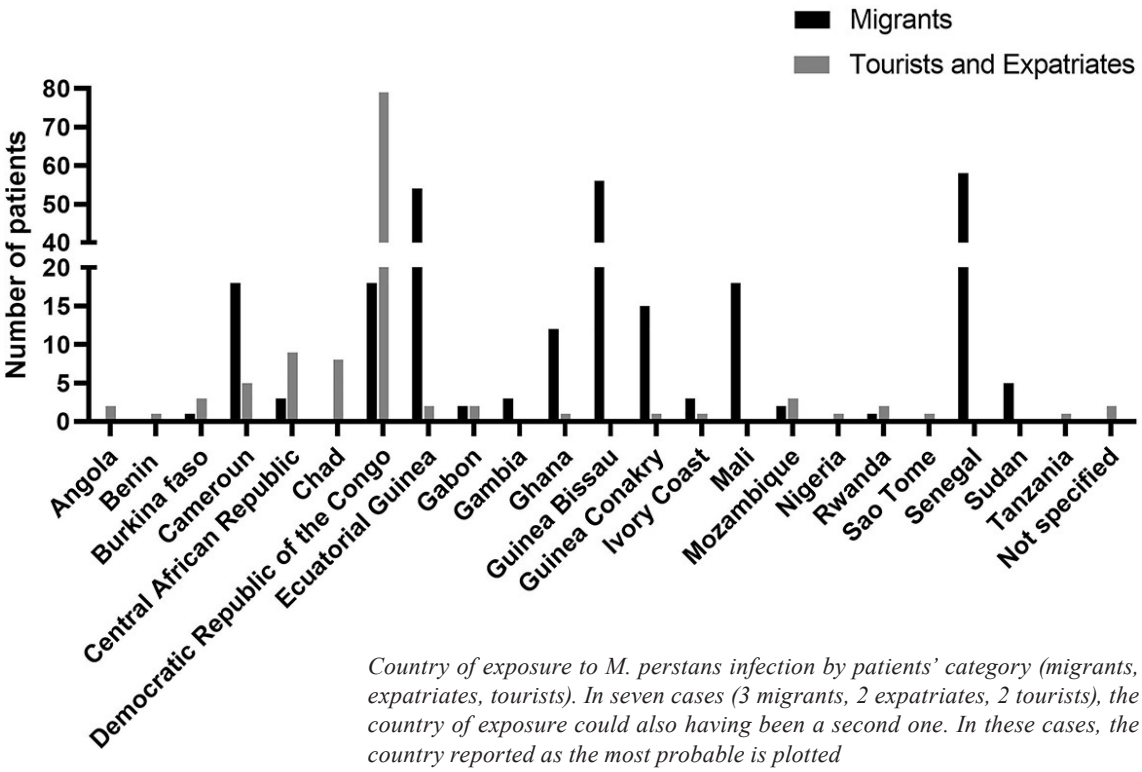
Infection with Mansonella perstans is a neglected filariasis, widely distributed in sub-Saharan Africa, characterized by an elusive clinical picture; treatment for mansonellosis is not standardized. This retrospective study aimed to describe the clinical features, treatment schemes and evolution, of a large cohort of imported cases of *M. perstans* infection seen in four European centres for tropical diseases.

Methods

Mansonella perstans infections, diagnosed by identification of blood microfilariae in migrants, expatriates and travellers, collected between 1994 and 2018, were retrospectively analysed. Data concerning demographics, clinical history and laboratory examinations at diagnosis and at follow-up time points were retrieved.

Results

A total of 392 patients were included in the study. 53.4% reported symptoms, abdominal pain and itching being the most frequent. Positive serology and eosinophilia were present in 84.4% and 66.1. Treatment was extremely heterogeneous: the most commonly used regimen was mebendazole for 1 month. 83.1% of patients having received treatment based on mebendazole and/or doxycycline, targeting Wolbachia, became amicrofilaremic. Lack of specific symptoms makes the clinical suspicion particularly difficult. Prospective studies are absolutely needed to optimize the clinical management.



Country of exposure to M. perstans infection by patients' category (migrants, expatriates, tourists). In seven cases (3 migrants, 2 expatriates, 2 tourists), the country of exposure could also having been a second one. In these cases, the country reported as the most probable is plotted

Publications

Tamarozzi F. et al, J Trav Med, 2022. https://doi.org/10.1093/jtm/taac048

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

LoaSpleen. Loa loa spleen lesions

- Project coordinator: DITM
- P.I. Federico Gobbi
- Start date: 2020
- End date: ongoing

Background and purpose

Loiasis, the infection with the vector-borne filarial nematode Loa loa, is widely distributed in central and west Africa. Long considered a rather benign infection, recently loiasis with high microfilarial burden was associated with increased mortality risk. Eyeworm and Calabar swelling are pathognomonic signs of the infection, but other atypical, non-specific manifestations can also occur. For instance, splenic nodules have been seldom reported. In this Grand Round, we report two cases of loiasis in migrants who presented with spleen nodules, which could be followed up over time (up to 27 months) with multiple imaging techniques until their resolution. We comment on the clinical implications of these observations, including differential diagnosis with similar imaging findings, and critically review the evidence of spleen involvement in loiasis and other filarial infections.

Methods

In this Grand Round, we report two cases of loiasis in migrants who presented with spleen nodules, which could be followed up over time (up to 27 months) with multiple imaging techniques until their resolution.

Results

In summary, it seems that, at least in natural host– parasite combinations in humans and monkeys, spleen granuloma formation could be a common process, the transient nature of which could explain their inconstant detection in imaging and post-mortem exams, similar to what is proposed for lung granuloma in Schistosoma spp infections.46–48 However, it remains to be elucidated whether nodules formation is a physiological mechanism of microfilariae elimination rarely observed because it is self-resolving, or it derives from some impaired function of healthy mechanisms, which results in less efficient microfilariae disintegration and granuloma formation, thus making microfilariae-containing granulomas detectable in some but not all individuals.

Publications

Tamarozzi F. et al, The Lancet Inf Dis, 2022. https://doi.org/10.1016/S1473-3099(21)00632-0

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

MigrantLoa. Loiasis from where you don't expect it.

- Project coordinator: DITM
- P.I. Federico Gobbi
- Start date: 2020
- End date: 2022
- Other institutions involved: University of Genova, Italy. Policlinico San Martino-IRCCS, Genoa, Italy.

Background and purpose

In the absence of pathognomonic signs, the diagnosis of filarial infections relies on geographical exposure and morphology of microfilariae, which requires expertise.

Methods

We present a case of loiasis in a patient not reporting exposure in areas of known *Loa loa* endemicity, namely Guinea Conakry.

Conclusion: With increasing migration and changing ecology, the occurrence of parasitic infections outside their 'classic' geographical distribution should be envisaged since missed diagnosis may have severe clinical consequences.

Publications

Nicolini AL et al, J Trav Med, 2022. https://doi.org/10.1093/jtm/taac060

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

g) Projects focused on schistosomiasis

UriSchis. Complicated urinary schistosomiasis, literature review. A TropNet study

- Project coordinator: University of Florence, Florence, Italy, DITM.
- DITM P.I. Federico Gobbi
- Other institutions involved: TropNet. Università di Milano, Italy. Hospital de Poniente, Almería, Spain. La Paz-Carlos III University Hospital, Madrid, Spain. University of Brescia and ASST Spedali Civili, Brescia, Italy. Vall d'Hebron University Hospital, Barcelona, Spain.
- Start date: 2021
- End date: 2022

Background and purpose

Schistosomiasis is a Neglected Tropical Disease (NTD) caused by trematodes of the genus Schistosoma. Schistosoma haematobium causes urogenital schistosomiasis (UGS), a chronic disease characterized by pathology of the urogenital tract leading to potentially severe morbidity for which the treatment is poorly standardized. We conducted a survey in TropNet centers on the clinical presentations and management strategies of complicated urogenital schistosomiasis (cUGS).

Methods

We reviewed the clinical records of patients seen at TropNet centers over a 20-year timespan (January 2001-December 2020). Case definition for cUGS included the presence of urogenital cancer, obstructive uropathy, kidney insufficiency of all grades, and female or male infertility with signs of genital involvement. Collected data included demographic information, patient category (traveller or migrant), imaging data, microbiological data (serology results and presence/absence of eggs in urine), histological features, and outcome at last visit recorded.

Results

Eight centres contributed with at least one case. Overall, 31 patients matched the inclusion criteria. Sub-Saharan Africa was the most likely place of infection for included patients. Median age was 30.6 years. Most patients were males. Hydronephrosis was the most frequent complication (58%) patients, followed by cancer (16.1%); 27 patients (87%) required surgical management. Use of praziquantel varied across

centres, with six different regimens employed. Very few cases of cUGSs were found, possibly indicating underdiagnosis. S. haematobium can cause considerable morbidity, with clinically challenging presentations requiring a multidisciplinary approach. Development of common protocols for early diagnosis and treatment is urgently needed.

Publications

Basile G et al, J Trav Med, 2022. https://doi.org/10.1093/jtm/taac150

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

DiagHepSchis. Diagnosis and clinical management of hepatosplenic schistosomiasis: A scoping review of the literature

- Project coordinator: DITM
- P.I. Federico Gobbi
- Other institutions involved: University Hospital, Düsseldorf, Germany.
- Start date: 2020
- End date: 2021

Background and purpose

Hepatosplenic schistosomiasis (HSS) is a disease caused by chronic infection with Schistosoma spp. parasites residing in the mesenteric plexus; portal hypertension causing gastrointestinal bleeding is the most dangerous complication of this condition. HSS requires complex clinical management, but no specific guidelines exist. We aimed to provide a comprehensive picture of consolidated findings and knowledge gaps on the diagnosis and treatment of HSS.

Methods

We reviewed relevant original publications including patients with HSS with no coinfections, published in the past 40 years, identified through MEDLINE and EMBASE databases. Treatment with praziquantel and HSS-associated pulmonary hyperten-

sion were not investigated. Of the included 60 publications, 13 focused on diagnostic aspects, 45 on therapeutic aspects, and 2 on both aspects.

Results

The most common diagnostic approaches to stratify patients based on the risk of variceal bleeding included the use of ultrasonography and platelet counts; on the contrary, evaluation and use of noninvasive tools to guide the choice of therapeutic interventions are lacking. Theray included beta-blockers, local management of esophageal varices, surgical procedures, and transjugular intrahepatic portosystemic shunt. Interventions were based of individual experiences and almost never rigorously compared. These results highlight a dramatic need for the implementation of rigorous prospective studies with long-term follow-up in different settings to fill such fundamental gaps, still present for a disease affecting millions of patients worldwide.

Publications

Tamarozzi F. et al, PLOS Negl Trop Dis, 2021. https://doi.org/10.1371/journal.pntd.0009191

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

SchistoTIPS. TIPS and splenorenal shunt for complications of portal hypertension in chronic hepatosplenic schistosomiasis. A case series.

- Project coordinator: University of Dusseldorf, Germany. Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany
- DITM P.I. Federico Gobbi
- Other institutions involved: University Hospital Bonn, Germany. University Hospital of Augsburg, Germany. University of Copenhagen, Denmark. University Clinic Frankfurt, Germany.
- Start date: 2020
- End date: 2021

Background and purpose

Transjugular intrahepatic portosystemic shunt (TIPS) and shunt surgery are established treatment options for portal hypertension, but have not been systematically evaluated in patients with portal hypertension due to hepatosplenic schistosomiasis (HSS), one of the neglected tropical diseases with major impact on morbidity and mortality in endemic areas.

Methods

In this retrospective case study, patients with chronic portal hypertension due to schistosomiasis treated with those therapeutic approaches in four tertiary referral hospitals in Germany and Italy between 2012 and 2020 were included. We have summarized pre-interventional clinical data, indication, technical aspects of the interventions and clinical outcome.

Results

13 patients with confirmed HSS were included. 11 patients received TIPS for primary or secondary prophylaxis of variceal bleeding due to advanced portal hypertension. In two patients, proximal splenorenal shunt surgery in combination with splenectomy was conducted. During follow-up (mean 23 months) no bleeding events were documented. In five patients, moderate and transient episodes of overt hepatic encephalopathy were observed. In one patient each, liver failure, portal vein thrombosis and catheter associated sepsis occurred after TIPS insertion. All complications and had favorable outcomes. TIPS implantation and shunt surgery are safe and effective options for (carefully selected) patients with advanced HSS in experienced

centers.

Publications

Nordmann T. et al, PLOS Negl Trop Dis, 2021. https://doi.org/10.1371/journal.pntd.0010065

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

SchistoDef. New Insights on Acute and Chronic vvSchistosomiasis.

- Project coordinator: DITM
- P.I. Federico Gobbi
- Other institutions involved: Leiden University Medical Centre, Leiden, The Netherlands. Institute of Tropical Medicine, Antwerp, Belgium. TropNet Schisto Task Force
- Start date: 2019
- End date: 2020

Background and purpose

A precise timeframe to differentiate acute schistosomiasis (AS) and chronic schistosomiasis (CS) is not well defined. Based on recent published literature, lung nodular lesions in AS and CS seem to have the same pathophysiology, that is, eggs laid in situ by adult worms, during an ectopic migration. Moreover, the occurrence of lung nodules due to clusters of eggs and the systemic immunoallergic reaction of AS (Katayama syndrome) may be two separate clinical entities, which may overlap during the early phase of infection. Consequently, the classical distinction between AS and CS loses much of its conceptual validity. If adult worms play a more important role in the early phase of the disease the clinical management of AS should probably be revised.

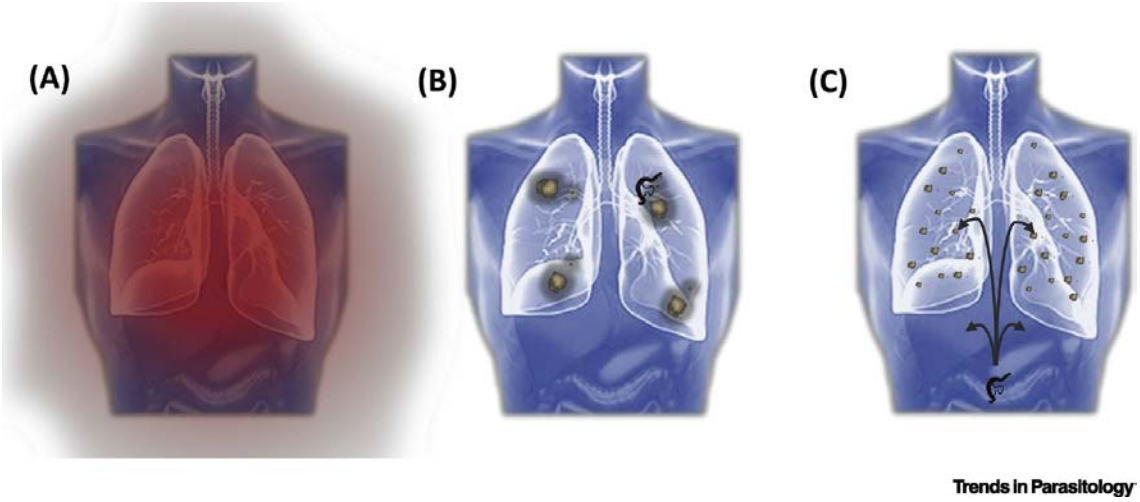
Methods

Based on recent published literature, as well as our own recent clinical experience with unusual presentations of schisotsomiasis in African Immigrants, we re-asses-

sed the current evidences on pathophysiology of acute and chronic schistosomiasis.

Results

Lung nodular lesions in AS and CS seem to have the same pathophysiology, eggs laid in situ by adult worms, during ectopic migration. This has practical implications. If adult worms are already present early after infection, then PZQ, in association with steroids, could be started at an earlier stage than generally recommended. PZQ would avoid novel oviposition, while steroids would attenuate the inflammatory reaction caused by already-laid eggs (and maybe adult decay). An important issue is that corticosteroids seem to decrease plasma levels of PZQ. Possibly, the association of steroids and PZQ during the early phase of infection, followed by PZQ for 1–3 days after several weeks, could be explored to overcome this initial interaction.



Lung Involvement in Different Phases of Schistosomiasis. (A) A very early systemic Loeffler-like reaction (Katayama syndrome), characterized, when present, by a diffuse interstitial pattern but no nodular lesions on imaging. This is possibly related to the migration of larvae/juvenile worms; the pulmonary symptoms are nonspecific and are part of a more general immunoallergic reaction. (B) Transient lung nodular lesions, most of the time asymptomatic and with a rather typical 'ground-glass' aspect on imaging; they may be present from the very early stage (3 weeks after infection) and throughout the whole period of active schistosomiasis (involving the presence of living adults). These are related to nests of eggs laid during sporadic adult migration. (C) Pulmonary arterial hypertension, with severe morbidity, occurs as a rather late complication of schistosomiasis. This is due to the granulomatous and fibrotic reaction around eggs embolized and stuck in capillaries, following their continuous release by adult worms established in the portal/caval venous system. In this case eggs are homogeneously distributed in the lungs.

Publications

Gobbi F. et al, Trends in parasitology, 2020. https://doi.org/10.1016/j.pt.2020.05.009

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

SchistoHybr. Molecular characterization of Schistosoma hybrids in bladder biopsies

- Project coordinator: University "Magna Graecia" of Catanzaro, Italy
- DITM P.I. Francesca Perandin
- Other institutions involved: Natural History Museum, London UK
- Start date: 2020
- End date: 2022

Background and purpose

Schistosomiasis is a neglected tropical disease affecting up to 90% of people living in Africa.[1] The emergence of natural inter *Schistosoma* species hybrids clearly highlights potential risks of mixing between human and animal infections, enhancing transmission and the spread of new strains. In particular, *Schistosoma haematobium* and *Schistosoma bovis* are closely related, are known to hybridize and also share snail intermediate hosts of the genus *Bulinus*. Atypical *Schistosoma haematobium* eggs were found in a bladder biopsy from an African migrant with severe Schistosomiasis. The *S. haematobium-bovis* hybrid diagnosis in patients plays an important role in explaining unusual morbidities and disease outcomes together with the potential risk of introduction into non-endemic areas.

Methods

Herein, to identify the potential presence of *S. haematobium-bovis* hybrids, we molecularly characterized typical and atypical eggs, presumed to be *S. haematobium*, collected from young African migrants.

Results

Amplification of mitochondrial (*cox 1*) and genomic (ITS2) DNA identified the presence of a *S. haematobium-Schistosoma bovis* hybrid. Phylogenetic analysis clustered the hybrid sequence with other sequences from western Africa.

Publications

Marascio N. et al, J Trav Med, 2022. https://doi.org/10.1093/jtm/taab194

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

h) Projects focused on treatment of NTD and other parasitic infections

MonoPar. Monoclonal antibodies for parasitic infection: a future reality or an utopic idea?

- Project coordinator: DITM
- P.I. Silvia Stefania Longoni
- Start date: 2021
- End date: 2021

Background and purpose

Following the SARS-CoV-2 pandemic, several clinical trials have been approved for the investigation of the possible use of mAbs, supporting the potential of this technology as a therapeutic approach for infectious diseases. The first monoclonal antibody (mAb), Muromonab CD3, was introduced for the prevention of kidney transplant rejection more than 30 years ago; since then more than 100 mAbs have been approved for therapeutic purposes. Nonetheless, only four mAbs are currently employed for infectious diseases. Protozoan infections are often neglected diseases for which effective and safe chemotherapies are generally missing.

Methods

In this review, we present the efforts that are being made in the evaluation of mAbs for the prevention or treatment of leishmaniasis, Chagas disease, malaria, and toxoplasmosis.

Results

mAbs are yet to be found useful in clinical practice for the treatment or prevention of protozoan infections. The main obstacles to the development of mAbs or Nbs therapies to parasitic diseases appear to be related to the production costs and the complexity of the host-pathogen interaction. Considering the rapidity of technology improvement in the development of biologicals, we can foresee that in the near future there would

be the possibility for the application of these therapies also for parasitic infections, provided that the preclinical and clinical research can better define the host-parasite mechanisms and reveal the key targets for a specific mAbs or Nbs treatment.

mAb	Disease	Molecular target	Type of ab	Trail phase	Study aim	Trial status*	Identifier
SCH708980	Visceral leishmaniasis	human IL-10	Humanized monoclonal antibody	Phase 1	To study the safety and effectiveness of SCH708980, alone and combined with AmBisome(Registered Trademark), as a treatment for visceral leishmaniasis	Withdrawn (Drug Product no longer available)	NCT01437020
VRC-MALMAB0100-00-AB (CIS43LS)	Malaria—*P. falciparum*	PfCSP—*P. falciparum* circumsporozoite protein	Human monoclonal antibody	Phase 2	To evaluate the safety, tolerability, and efficacy of VRC MALMAB0100-00-AB (CIS43LS) against naturally occurring Plasmodium falciparum (Pf) infection	Recruiting	NCT04329104
VRC-MALMAB0100-00-AB (CIS43LS)	Malaria—*P. falciparum*	PfCSP—*P. falciparum* circumsporozoite protein	Human monoclonal antibody	Phase 1	To evaluate safety and tolerability of different dosages of VRC MALMAB0100-00-AB (CIS43LS) in healthy malaria-naive individuals, as well as the protection against *P. falciparum* following Controlled Human Malaria Infections (CHMI)	Recruiting	NCT04206332
TB31F	Malaria—*P. falciparum*	Pfs48/45, gametocyte surface protein	Humanized monoclonal antibody	Phase 1	To assess the safety and tolerability of mAb TB31F administered intravenously or subcutaneously in healthy, malaria naïve, adults	Completed, results not yet available	NCT04238689

**Info as per July 17th, 2021.*
Data retrieved from ClinicalTrials.gov.

mAb evaluated in clinical trials for protozoan diseases treatment.

Publications

LongoniSSetal,FrontiersinMedicine,2021.https://doi.org/10.3389/fmed.2021.745665

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

EchinAlb. Continuous albendazole treatment regimen for human echinococcal infections

- Project coordinator: DITM
- P.I. Francesca Tamarozzi
- Start date: 2020
- End date: 2020

Background and purpose

Cystic (CE) and alveolar (AE) echinococcosis are chronic, neglected parasitic diseases burdened by high morbidity and, for AE, by high mortality, if left untreated. CE and AE have a widespread distribution, including Europe. Albendazole (ABZ), a broad-spectrum benzimidazole drug widely used to treat parasitic infections, is the drug of choice for the management of CE and AE, and is parasitostatic on echinococcal metacestodes. In Europe, ABZ is licensed for interrupted "cyclic" treatment, for a maximum of 3 cycles. However, better efficacy with no increased side effects has been shown when the drug is administered continuously and for longer periods.

Methods

In this viewpoint, we compare current schedules for the treatment of CE and AE in Europe with existing guidelines.

Results

Current international recommendations recommend continuous administration of ABZ for months to years for the treatment of CE and AE. However, in Europe this schedule, with the exception of France, is "off-label". Adding to the very high cost of the drug and frequent "out-of-stock" situation, these conditions put patients with CE and AE regularly at risk of treatment discontinuation and disease progression. We urge a coordination between stakeholders to find effective and feasible ways to take action to revise the benzimidazole dosage regimens for CE and AE and to ensure a fair, regular, and easy access to the appropriate treatment to those suffering from these serious diseases.

Publications

Tamarozzi F et al, PLOS Negl Trop Dis, 2020. https://doi.org10.1371/journal.pntd.0008566

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

i) Projects focused on the study of other rare infectious diseases according to the Italian Ministry of Health definition: Whipple Disease and leprosy

LepRef. Leprosy in Refugees and Migrants in Italy and a Literature Review of Cases Reported in Europe between 2009 and 2018

- Project coordinator: DITM
- P.I.: Anna Beltrame
- Other institutions involved: IRCCS Policlinico San Martino, Genoa, Italy

Background and purpose

Leprosy is a chronic neglected infectious disease that affects over 200,000 people each year and causes disabilities in more than four million people in Asia, Africa, and Latin America. The disease can appear with a wide spectrum of clinical forms, and therefore the clinical suspicion is often difficult. Refugees and migrants from endemic countries affected by leprosy can remain undiagnosed in Europe due to the unpreparedness of clinicians. Continents of origin were Africa (42%), Asia (40%), and South and Central America (18%). The symptoms reported were skin lesions (91%), neuropathy (71%), edema (7%), eye involvement (6%), fever (6%), arthritis (4%), and lymphadenopathy (4%). Seven patients (13%) had irreversible complications. Overall, 35% were relapses and 66% multibacillary leprosy. Furthermore, we conducted a review of 17 case reports or case series and five nationwide reports, published in the same decade, describing 280 migrant patients with leprosy in Europe. In Europe, leprosy is a rare chronic infectious disease, but it has not completely disappeared. Diagnosis and treatment of leprosy in refugees and migrants from endemic countries are a challenge. European guidelines for this neglected disease in this high-risk population would be beneficial.

Methods

We retrospectively describe the characteristics of 55 refugees/migrants with a diagnosis of leprosy established in Italy from 2009 to 2018.

Results

Continents of origin were Africa (42%), Asia (40%), and South and Central America (18%). The symptoms reported were skin lesions (91%), neuropathy (71%), edema (7%), eye involvement (6%), fever (6%), arthritis (4%), and lymphadenopathy (4%). Seven patients (13%) had irreversible complications. Overall, 35% were relapses and 66% multibacillary leprosy. Furthermore, we conducted a review of 17 case reports or case series and five nationwide reports, published in the same decade, describing 280 migrant patients with leprosy in Europe. In Europe, leprosy is a rare chronic infectious disease, but it has not completely disappeared. European guidelines for this neglected disease in this high-risk population would be beneficial.

Publications

Beltrame A., et al, Microorganisms, 2020. https://doi.org/10.3390/microorganisms8081113

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

TrophWhip. From Tropheryma whipplei colonization to an early diagnosis of Classic and Localized Whipple's disease

- Project coordinator: DITM
- P.I. Anna Beltrame
- Start date: 2019
- End date: 2021

Background and purpose

Tropheryma whipplei, a bacterium of the order of *Actinomycetales* (1), causes Whipple's disease (arthritis followed by diarrhea and weight loss) (2-8), as well as acute (fever, pneumonia, diarrhea) (9-16) and chronic (endocarditis, arthritis, CNS involvement, uveitis and other) manifestations (17-21).*T. whipplei* intestinal colonization has been described in asymptomatic healthy subjects (22). The colonization rate seems to vary according to the geographical area, as well as to age and to a number of risk factors (poor hygiene and sanitary conditions or immunodeficiency). In Italy, althou-

gh Whipple's disease is reported as a rare disease as its prevalence in the general population is 3/106 (36), there are no data regarding the prevalence of *T. whipplei* stool colonization in the autochthonous population nor in immigrant population living in Italy. Furthermore, no studies are available on coinfection between *T. whipplei* and other protozoa except *G. duodenalis*. Aim: To obtain the first molecular epidemiological survey of Tropheryma whipplei intestinal colonization in Italy.

Methods

Retrospective, observational study to assess the prevalence of T. whipplei, the causative agent of Whipple's disease, in stool samples (real-time PCR) of patients attending the Center for Tropical Diseases (Italy) and risk factors associated.

Results

Overall prevalence was 6.9% (85/1240). The younger age group showed a significantly higher rate than older age group (12.7 vs 5.9%, p = 0.002). The prevalence was 4.9% for Italians and 9.3% for migrants (p = 0.003). Among the latter, children less than 10 years had higher prevalence than older ones (17.3 vs 7.3%, p = 0.003). The young age, male gender and *Giardia duodenalis* and *Entamoeba histolytica* coinfection were risk factors. Our study confirms an increased risk of acquiring T. whipplei infection during childhood, under poor sanitary conditions.

Table 2. Absolute and age-specific prevalence of *Tropheryma whipplei* intestinal colonization, stratified by geographical area of birth.

T. whipplei PCR positive	Age groups			p-value
	All ages	<10 years old	≥10 years old	
Total, n/N (%)	85/1240 (6.9)	23/181 (12.7)	62/1059 (5.9)	0.002
Italian group, n/N (%)	34/694 (4.9)	4/71 (5.6)	30/623 (4.8)	0.770
Non-Italian group, n/N (%)	51/546 (9.3)	19/110 (17.3)	32/436 (7.3)	0.003
Africa	34/304 (11.2)	11/57 (19.3)	23/247 (9.3)	0.038
Europe	1/55 (1.8)	0/6 (0.0)	1/49 (2.1)	–
America	11/102 (10.8)	5/20 (25.0)	6/82 (7.3)	0.037
Asia	5/85 (5.9)	3/27 (11.1)	2/58 (3.5)	0.320

Publications

Beltrame A. et al, Future Microbiology, 2019. https://doi.org/10.2217/fmb-2018-0347

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

TrophHeli. Tropheryma whipplei, Helicobacter pylori and Intestinal Protozoal Co-Infections in Italian and Immigrants

- Project coordinator:
- DITM P.I. Anna Beltrame
- Start date: 2019
- End date: 2021

Background and purpose

Tropheryma whipplei (TW), *Helicobacter pylori* (HP), and intestinal protozoa (IP) are widespread pathogens with similar routes of transmission and epidemiological risk factors. Epidemiological data on co-infection between TW, HP, and IP are scarce. We aimed to more deeply investigate the co-infection rate for these pathogens, evaluating the risk factors and symptoms.

Methods

This was a cross-sectional study conducted at the IRCCS Sacro Cuore Don Calabria Hospital in Northern Italy, a referral center for tropical and Whipple's disease (WD). Stored stool samples from 143 subjects previously tested for TW DNA by real-time PCR were explored for HP and IP DNA detection. The virulence factor *cagA* was investigated in HP-positive patients.

Results

A history of migration was reported significantly more in TW-positive than in negative subjects (34.1% vs. 9.1%, $p = 0.001$) and in HP-infected than in non-infected (59.1% vs. 9.1%, p < 0.001). HP infection rate differed significantly between TW-infected and uninfected groups (31.8% vs. 8.1%, $p = 0.001$), while no difference was observed for IP infection. Higher TW intestinal colonization was found in HP-infected patients than in non-infected (63.6% vs. 24.8%, $p = 0.001$). *Blastocystis* infection was more frequent in HP-infected (40.9% vs. 17.4%, $p = 0.018$).

Publications

Moro L. et al, Microorganisms, 2022. https://doi.org/10.3390/microorganisms10040769

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

TrophIran. Tropheryma whipplei intestinal colonization in immunocompromised children in Iran

- Project coordinator: University of Medical Sciences, Qom, Iran.
- DITM P.I. Anna Beltrame
- Other institutions involved: Pasteur Institute of Iran
- Start date: 2020
- End date: 2021

Background and purpose

Tropheryma whipplei causes Whipple's disease. Children are reservoirs of this bacterium. The aim of this study was to investigate the presence of *T. whipplei* in children with immunodeficiency in central Iran from July 2018 to February 2019.

Methods

Stool samples were tested by SYBR Green and Taq-Man real-time PCR assays. For confirmation, the isolated DNA was sequenced.

Results

One hundred and thirty children were enrolled. Acute lymphocytic leukemia was the most reported immunodeficient disease (77%), followed by non-Hodgkin lymphoma and retinoblastoma. Thirteen (10%) children had *T. whipplei* DNA in the stool; 11.4% of the children under 5 years old were positive. This is the first study showing the circulation of *T. whipplei* in Iran.

Publications

Shams S. et al, Future Microbiology, 2021. https://doi.org/10.2217/fmb-2021-0091

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

Macro-project 2: Unravelling the pathophysiology bases and developing of new diagnostic approaches for neglected tropical diseases

a) Projects focused on improving the diagnostic approach and pathophysiology knowledge of *Strongyloides stercoralis* infection

StrongNIE. Diagnostic accuracy of a novel immunoassay for Strongyloides stercoralis

- Project coordinator: DITM
- P.I. Dora Buonfrate
- Start date: 2020
- End date: 2021

Background and purpose

The diagnosis of strongyloidiasis is challenging. Serological tests are acknowledged to have high sensitivity, but issues due to cross-reactions with other parasites, native parasite antigen supply and intrinsic test variability do occur. Assays based on recombinant antigens could represent an improvement. The aim of this study was to assess the sensitivity and specificity of two novel immunoglobulin (Ig)G and IgG4 enzyme-linked immunosorbent assays (ELISAs) based on the recombinant antigens NIE/SsIR for the diagnosis of strongyloidiasis.

Methods

This was a retrospective diagnostic accuracy study. We included serum samples collected from immigrants from strongyloidiasis endemic areas for whom there was a matched result for *Strongyloides stercoralis* on agar plate culture and/or PCR assay, or a positive microscopy for *S. stercoralis* larvae. For the included samples, results were also available from an in-house indirect fluorescent antibody test (IFAT) and a commercial (Bordier ELISA; Bordier Affinity Products SA) ELISA. We excluded: (i) samples with insufficient serum volume; (ii) samples from patients treated with ivermectin in the previous 6 months; and (iii) sera from patients for whom only routine coproparasitology was performed after formol–ether concentration, if negative

for *S. stercoralis* larvae. The performance of the novel assays was assessed against: (i) a primary reference standard, with samples classified as negative/positive on the basis of the results of fecal tests; (ii) a composite reference standard (CRS), which also considered patients to be positive who had concordant positive results for the IFAT and Bordier ELISA or with a single "high titer" positive result for the IFAT or Bordier ELISA. Samples with a single positive test, either for the IFAT or Bordier ELISA, at low titer, were considered to be "indeterminate," and analyses were carried out with and without their inclusion.

Results

When tested against the CRS, the IgG ELISA performed best, with 78% sensitivity (95% CI: 72-83%) and 98% specificity (95% CI: 96-100%), when a cut-off of 0.675 was applied and the indeterminate samples were excluded from the analysis. The NIE-S-sIR IgG ELISA demonstrated better accuracy than the IgG4 assay and was deemed promising particularly for serosurveys in endemic areas.

Publications

Tamarozzi F. et al, Parasites & Vectors, 2021. https://doi.org/10.1186/s13071-021-04916-x

Funding

Fondo Ricerca Corrente, Italian Ministry of Health

StrongRap. Accuracy of a rapid diagnostic test for the detection of Strongyloides stercoralis infection

- Project coordinator: DITM
- P.I. Dora Buonfrate
- Other institutions involved: Universiti Sains Malaysia, Malaysia.
- Start date: 2021
- End date: ongoing

Background and purpose

Strongyloidiasis, a nematode infection which is mainly caused by *Strongyloides stercoralis* in humans, can lead to a fatal syndrome in immunocompromised individuals.

A rapid diagnostic test would be helpful for screening purposes. The aim of this study was to estimate the accuracy of a novel immunochromatographic test (ICT) for the diagnosis of *S. stercoralis* infection.

Methods

A single-centre diagnostic accuracy study was undertaken using well-characterized frozen sera available from the biobank of a referral hospital for parasitic diseases in Italy. The included sera were from migrants from sub-Saharan Africa, and matching results were available for agar plate culture and/or polymerase chain reaction for *S. stercoralis*; moreover, the results of both a commercial enzyme-linked immunosorbent assay test and an in-house immunofluorescence test for strongyloidiasis were made available. Laboratory staff who read the ICT results were blinded as regards the results of the other tests. Two readers independently read the ICT, and a third one was involved when results were discrepant. The accuracy of the ICT was assessed both against the results of the panel of faecal tests and by latent class analysis (LCA).

Results

Agreement between the readers was excellent [Cohen's = 92.7%, 95% confidence interval (CI) 88.3-97.1%]. When assessed against the results of the faecal tests, the sensitivity and specificity of the ICT were 82.4% (95% CI 75.7-89.0%) and 73.8% (95% CI 66.8-80.9%), respectively. According to the LCA, the sensitivity and specificity were 86.3% (95% CI 80.1-92.5%) and 73.9% (95% CI 67.0-80.8%), respectively.

Publications

Tamarozzi F. et al, Parasites & Vectors, 2022. https://doi.org/10.1186/s13071-022-05249-z

Funding

Fondo Ricerca Corrente, Italian Ministry of Health

StrongRNA. Identification of miRNA of Strongyloides stercoralis

- Project coordinator: DITM
- P.I. Elena Pomari
- Other institutions involved: Università di Verona, Italy. Università di Parma, Italy
- Start date: 2020
- End date: 2022

Background and purpose

There is no gold standard for diagnosing strongyloidiasis, and infections are frequently misdiagnosed. A better understanding of the molecular biology of this parasite can be useful for example for the discovery of potential new biomarkers. Interestingly, recent evidence showed the presence of small RNAs in Strongyloididae, but no data was provided for S. stercoralis. In this study, we present the first identification of miRNAs of both L1 and iL3 larval stages of S. stercoralis. For our purpose, the aims were: (i) to analyse the miRNome of L1 and iL3 S. stercoralis and to identify potential miRNAs of this nematode, (ii) to obtain the mRNAs profiles in these two larval stages and (iii) to predict potential miRNA target sites in mRNA sequences.

Methods

Total RNA was isolated from L1 and iL3 collected from the stool of 5 infected individuals. For the miRNAs analysis, we used miRDeep2 software and a pipeline of bio-informatic tools to construct a catalog of a total of 385 sequences. Among these, 53% were common to S. ratti, 19% to S. papillosus, 1% to Caenorhabditis elegans and 44% were novel.

Results

Using a differential analysis between the larval stages, we observed 6 suggestive modulated miRNAs. Along with this analysis, we obtained also the mRNAs profiles in the same samples of larvae. Multiple testing found 81 statistically significant mRNAs. Finally, we found 33 predicted mRNA targets of the modulated miRNAs, providing relevant data for a further validation to better understand the role of these small molecules in the larval stages and their value in clinical diagnostics.

Publications

Pomari E. et al, Scientific Reports, 2022. https://doi.org/10.1038/s41598-022-14185-y

Funding

Fondo Ricerca Corrente, Italian Ministry of Health

StrongImm. Systemic profile of immune factors in chronic strongyloidiasis

- Project coordinator: DITM
- P.I. Natalia Tiberti
- Other institutions involved: Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.
- Start date: 2019
- End date: 2020

Background and purpose

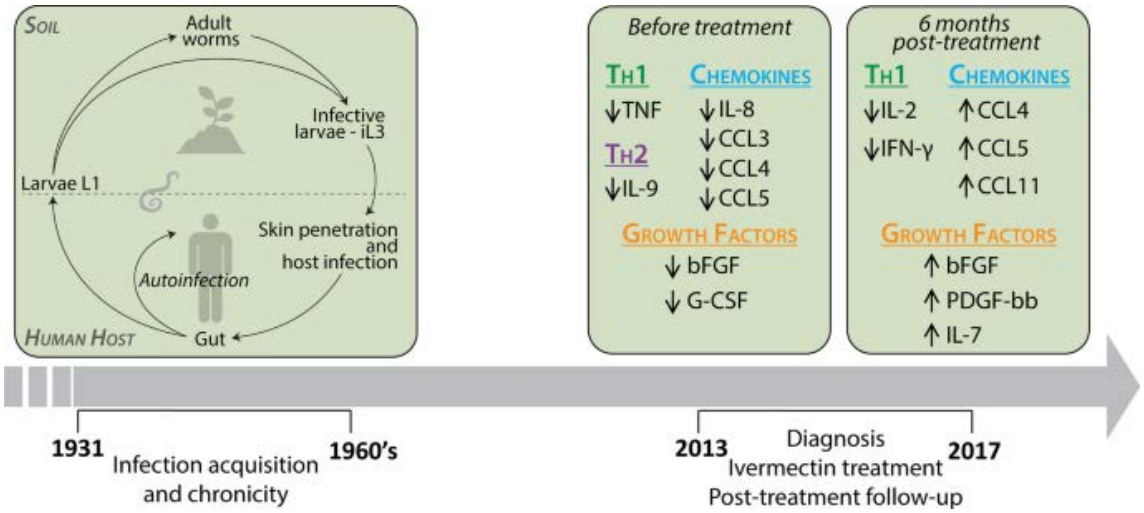
Strongyloidiasis caused by Strongyloides stercoralis is a soil-transmitted helminthiasis affecting an estimated 370 million people and considered one of the most neglected tropical diseases. Although mostly distributed in tropical and subtropical areas, autochthonous infections have also been documented in north-eastern Italy, even though the transmission presumably stopped decades ago. Because of its peculiar auto-infective cycle, strongyloidiasis can persist lifelong, but the pathophysiological mechanisms associated with the maintenance of such a chronic infection are yet to be fully deciphered.

Methods

Serum levels of 23 immune factors were retrospectively assessed in a subgroup of participants in a randomised clinical trial for the treatment of strongyloidiasis (Strong Treat). Here we included Italian subjects born between 1931 and 1964 and diagnosed with strongyloidiasis between 2013 and 2017 (Ss^+, n = 32). Serum samples obtained before (BT) and 6 months (6M AT) after ivermectin treatment, as well as from age- and gender-matched uninfected controls (CTRL, n = 34) were analysed.

Results

The assessed immune factors showed a general reduced concertation in Ss+ patients. We observed chemokines as particularly affected by the presence of the parasite, since IL-8, CCL3, CCL4 and CCL5 were significantly reduced, suggesting that immune cell recruitment to the infection site might be dampened in these patients. A raised concentration of three growth factors, bFGF, PDGF-BB and IL-7 was observed post-treatment. S. stercoralis might suppress host responses that could otherwise result in its ejection. Our results offer novel insights in the potential mechanisms of disease tolerance that might take place during this chronic infection, including a potential T-cell hypo-responsiveness and a role for chemokines.



In our cohort the assessed immune factors showed a lack ofassociation with eosinophilia and Th 1 and Th2 cytokines were mostly unaltered. Chemokines were significantly reduced in concentration in population affected by chronic strongyloidiasis, suugesting that immune cell recruitment to the infection site might be dampened in these patients. This observation was restored after the treatment indicating parasite involvement in immune impairement

Publications

Tiberti N. et al, Parasites & Vectors, 2020. https://doi.org/10.1186/s13071-020-04391-w

Funding

Fondo Ricerca Corrente, Italian Ministry of Health

b) Projects focused on improving the diagnostic approach and pathophysiology knowledge of other NTDs and rare diseases

FilariaPCR. Preliminary evaluation of an in house real-time PCR for the detection of human filariasis

- Project coordinator: DITM
- P.I. Fabio Formenti
- Other institutions involved: Instituto de Salud Carlos III, Madrid, Spain.
- Start date: 2019
- End date: 2022

Background and purpose

Infections with the filarial nematodes Loa loa and Mansonella perstans are among the most neglected filarial infections. L. loa is endemic in 11 countries of Central and West Africa and loiasis is estimated to affect about 20 million people. M. perstans infection is widespread in more than 30 countries of sub-Saharan Africa. Due to the difficulty in diagnosing loiasis and M. perstans mansonellosis on a clinical basis, the diagnosis of infection with *L. loa* and *M. perstans* relies on laboratory techniques. Definitive diagnosis is based on the detection, identification, and quantification of circulating microfilariae (mf) by microscopy of concentrated blood. However, this is impractical for screening purposes as it requires expert laboratory personnel, considerable blood manipulation, and is time consuming, especially for the final issue of negative result reports, which are very common in the population visited outside endemic areas. The aim of the current work is the preliminary evaluation of the performance of the in-house real-time PCR described by Ta and colleagues compared to the routine microscopic approach for the screening of filarial infections in the clinical setting outside endemic areas.

Methods

This is an exploratory, retrospective study conducted on 59 human blood samples collected between 2017 and 2018 obtained pre-treatment from patients coming from Sub-Saharan Africa (Guinea Bissau, Nigeria, Ghana, Cameroon, Senegal, Cote d'ivoire, Chad) with positive filarial serology and available in the biobank of the Department of InfectiousTropical Diseases and Microbiology (DITM) of IRCCS Sacro Cuore Don Calabria Hospital, Negrar, Verona, Italy. A multiplex-pan filarial real-time

PCR targeting ITS1 was applied, as described by Ta el al, with some minors modifications in the sequence of the primers as well as the annealing temperature.

Table 4
Statistical values obtained for the qPCR method for each filarial species separately.

	Multiplex-pan filarial real-time PCR for *L. loa*	Multiplex-pan filarial real-time PCR for *M. perstans*
Sensitivity % (95% CI)	100% (100%-100%)	69.2% (44.1%-94.3%)
Specificity % (95% CI)	100% (100%-100%)	97.8% (93.6%, 102.0%)
PPV % (95% CI)	100% (100%-100%)	90.0% (71.4%, 108.6%)
NPV % (95% CI)	100% (100%-100%)	91.8% (84.2%, 99.5%)
Kappa index % (95% CI)	100% (100%-100%) very good agreement	73.1% (50.6%-95.7%) good agreement

PPV: positive predictive value. NPV: negative predictive value. CI: confidence interval

Results

The species identification was 100% concordant between molecular analysis and microscopy, there were not any discordancy at the level of filarial species identification. All the patients microscopically diagnosed as L. loa, were detected as L. loa by multiplex-pan filarial qPCR, likewise it occurred with M. perstans mf-positive patients. Compared to microscopy, therefore, the multiplex-pan filarial realtime PCR had 75% sensitivity and 98 % specificity. However, if statistical values were calculated separately for each species, the multiplex-pan filarial real-time PCR had a high sensitivity and specificity for detecting L. loa species, but a poor sensitivity and a high specificity for M. perstans.

Publications

Formenti F. et al, Acta Tropica, 2021. https://doi.org/10.1016/j.actatropica.2021.105838

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

DiagLoa. Performance of two serodiagnostic tests for loiasis in a Non-Endemic area

- Project coordinator: DITM
- P.I. Federico Gobbi
- Other institutions involved: INSERM Montpellier, France. Drugs & Diagnostics for Tropical Diseases, San Diego, California, United States of America. Istituto Superiore di Sanità, Rome, Italy.
- Start date: 2019
- End date: 2020

Background and purpose

Loiasis, caused by the filarial nematode Loa loa, is endemic in Central and West Africa where about 10 million people are infected. There is a scarcity of convenient, commercial diagnostics for L. loa.

Methods

We retrospectively compared the performance of a Loa Antibody Rapid Test (RDT) and a commercial ELISA pan-filarial test on 170 patients, 65 with loiasis [8 with eyeworm, 29 with positive microfilaremia, 28 with neither microfilaremia nor history of eyeworm but eosinophilia and history of Calabar swelling (probable loiasis)], 95 with other common parasitic infections and no previous exposure to L. loa.

Results

The sensitivity of the RDT and of the ELISA were 93.8%and 90.8%, respectively. For the RDT, most of the cross-reactions were observed in patients with M. perstans. None of the 27 subjects infected with intestinal nematodes was found positive at this test. The ELISA is meant to be a pan-filarial assay, and reacted extensively with cases of M. perstans (95%), as expected, and also in 11/18 (61.1%) patients with strongyloidiasis and in 3/5 (60%) with hookworm infection. The RDT and the ELISA are both highly sensitive for the diagnosis of loiasis. Considering that the RDT is specifically meant for Loa loa infection, and its high sensitivity, this test could be a useful tool for the diagnosis of occult loiasis.

Publications

Gobbi F. et al, PLOS Negl Trop Dis, 2020. https://doi.org/10.1371/journal.pntd.0008187

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

ChagasPCR. Evaluation of an in house versus a commercial real-time PCR for Trypanosoma cruzi detection

- Project coordinator: DITM
- P.I. Stefania Longoni
- Other institutions involved: University of Florence, Italy.
- Start date: 2019
- End date: 2020

Background and purpose

Chagas disease, a neglected protozoal disease endemic in Latin America, is also currently considered an emerging threat in nonendemic areas because of population movements. The detection of *Trypanosoma cruzi* DNA is increasingly being considered as important evidence to support Chagas disease diagnoses. However, further performance evaluation of molecular assays is useful for a standardization of strategy considering the whole process in routine diagnosis, especially for the different settings such as endemic and nonendemic countries.

Methods

Seventy-five samples were collected from subjects screened for Chagas disease in Italy. The DNA was isolated from blood using automated extraction. We evaluated the performance of the commercial RealCycler CHAG kit (pmPCR) based on satellite DNA (SatDNA) and of an in-house real-time PCR (ihPCR) targeting Sat and kinetoplast (k) DNAs, using the concordance of two serology assays as a reference standard.

Results

The sensitivity of kDNA and SatDNA tests by ihPCR and SatDNA by pmPCR were 14.29% (95% confidence interval (CI) 6.38 to 26.22), 7.14% (95% CI 1.98 to 17.29), and 7.14% (95% CI 1.98 to 17.29), respectively. Specificity was 100% for all PCR assays and targets. Overall, our results suggest that the preferred approach for clinical laboratories is to combine the kDNA and SatDNA as targets in order to minimize false-negative results increasing sensitivity.

Publications

Longoni SS et al, microorganisms, 2020. https://doi.org/10.3390/microorganisms8111692

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

SchistoCAA. Evaluation of microscopy, serology, circulating anodic antigen (CAA), and eosinophil counts for the follow-up of migrants with chronic schistosomiasis: a prospective cohort study

- Project coordinator: DITM
- P.I. Francesca Tamarozzi
- Other institutions involved: Leiden University Medical Centre, Leiden, The Netherlands.
- Start date: 2020
- End date: 2021

Background and purpose

Anaccuratetestforthediagnosisandpost-treatmentfollow-upofpatientswithschistosomiasis is needed. We assessed the performance of different laboratory parameters, including the up-converting reporter particle technology lateral flow assay to detect circulating anodic antigen (UCP-LF CAA), for the post-treatment follow-up of schistosomiasis in migrants attending a dedicated outpatient clinic in a non-endemic country.

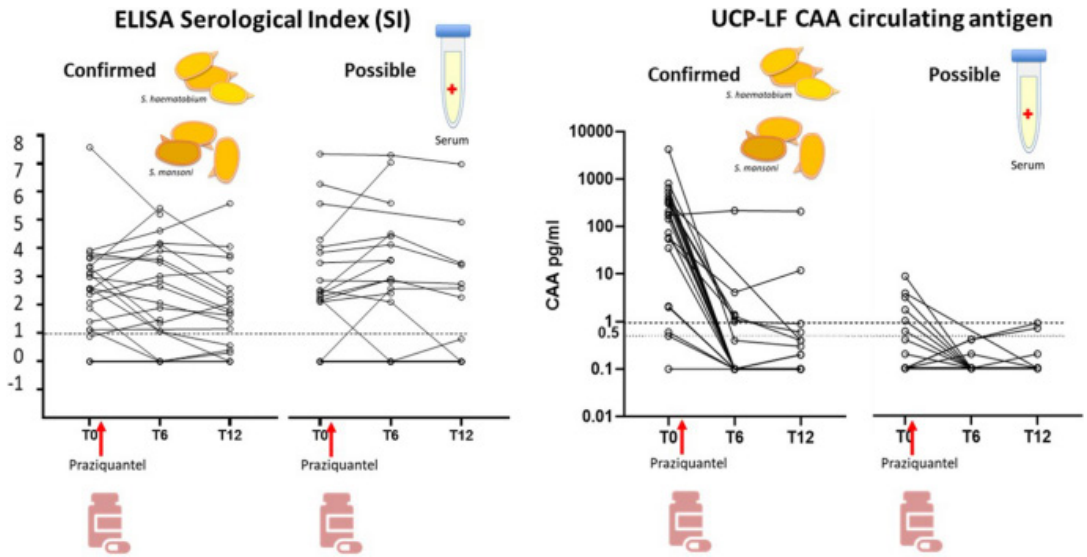
Methods

Routine anti-Schistosoma serology results and eosinophil counts were obtained of patients with positive urine/stool microscopy and/or PCR (confirmed cases) or only positive serology (possible cases), and at least one follow-up visit at 6 (T6) or 12 (T12) months after praziquantel treatment. All sera samples were tested with the UCP-LF CAA assay.

Results

Forty-eight patients were included, 23 confirmed and 25 possible cases. The percentage seropositivity and median antibody titers did not change significantly during follow-up. UCP-LF CAA was positive in 86.9% of confirmed and 20% of possi-

ble cases. The percentage positivity and median CAA levels decreased significantly post-treatment, with only two patients having positive CAA levels at T12. Conclusions: The UCP-LF CAA assay proved useful for the diagnosis of active infection with Schistosoma spp. and highly valuable for post-treatment monitoring in migrants, encouraging the development of a commercial test.



Publications

Tamarozzi F et al, Parasites & Vectors, 2021. https://doi.org/10.1186/s13071-021-04655-z

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

SchistoRDT. Preliminary evaluation of a new Schistosoma Immunochromatographic Test.

- Project coordinator: DITM
- P.I. Silvia Stefania Longoni
- Start date: 2020
- End date: 2021

Background and purpose

Over 90% of schistosomiasis infections occur in sub-Saharan Africa. A rapid ICT test would be a cheap and easy tool that could be used also in the field. We preliminarily evaluated the performance of a new Schistosoma black-latex based IgG-IgM ICT (Black-ICT) on serum samples.

Methods

We calculate the cut-off using optimized O.D. thresholds, generated by receiver operating characteristics (ROC) curve analysis, testing 39 well-characterized sera obtained from lepromatous leprosy patients with strongly positive ND-O-BSAELISA titer and 39 sera from healthy non-endemic patients never exposed to *M. leprae or M. tuberculosis*. Indeed, we tested a second set of sera from suspected or confirmed leprosy or household contacts (SLALT group, n=50), and patients with tuberculosis (control group, n=40).

Results

The results indicate a high sensitivity (98.0%) but the specificity depends on the application of a cut-off value that can discriminate between positive and negative samples. Considering a possible direct application of this test on blood from finger prick, the results are promising, provided that a signal intensity scale is developed, guiding the result interpretation.

Publications

Longoni SS et al, Acta Tropica, 2021. https://doi.org/10.1016/j.actatropica.2021.105893

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

SchistoEco. Prospective cohort study using ultrasonography of Schistosoma haematobium-infected migrants

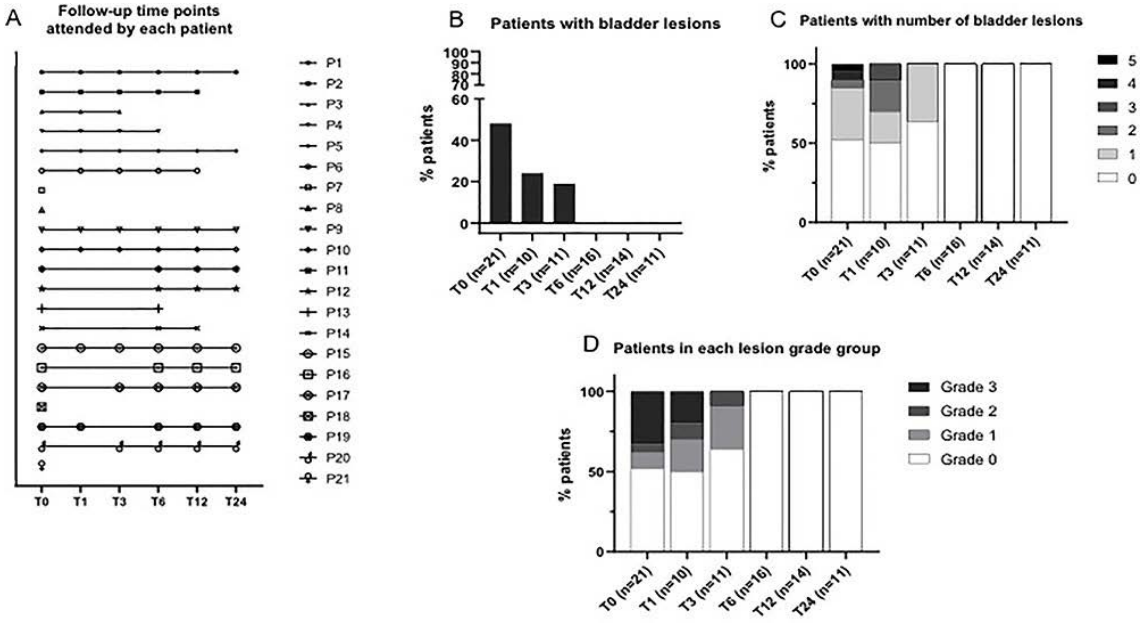
- Project coordinator: DITM
- P.I. Francesca Tamarozzi
- Start date: 2020
- End date: 2021

Background and purpose

Chronic infection with Schistosoma haematobium may lead to serious complications, including bladder carcinoma. Although it is recommended that only bladder masses not regressing within 6 months after praziquantel intake should be investigated invasively, cystoendoscopy is still often performed at diagnosis even in the absence of further signs of concern. No prospective study so far evaluated the evolution of bladder lesions after treatment in case of no risk of reinfection, which could inform case management.

Methods

Adult African migrants with active S. haematobium infection, as assessed by positive urine PCR or microscopy for eggs in urine or bladder biopsy, underwent urinary tract ultrasound at enrolment and at 1, 3, 6, 12 and 24 months after praziquantel treatment. Patients in advanced pregnancy or with known Schistosoma-unrelated chronic pathology of the urinary tract were excluded.



UltraSonography (US) examination of the bladder at T0 and during follow-up. P-number = patient code. T-number = follow-up time point in months; numbers in bracket indicate number of patients attending the time point visit. A. Follow-up time points attended by each patient. B. Percentage of patients with bladder lesions visible on US at enrolment and at each follow-up time point. C. Percentage of patients having 0 up to 5 (maximum number observed) bladder lesions on US at enrolment and at each follow-up time point. D. Percentage of patients having Grade 0 (no lesions visible on US) up to Grade 3 (maximum thickening ≥10 mm) at enrolment and at each follow-up time point.

Results

Twenty-one patients participated; ten had bladder masses on ultrasound. Follow-up ≥6 months was completed by 16 patients; ≥12 months by 14 and 24 months by 11. All patients with bladder lesions on enrolment completed a follow-up of ≥6 months. Lesions resolved completely by 6 months in all cases. This is the first prospective, long-term follow-up study with ultrasound of patients with urinary schistosomiasis outside endemic areas. Mucosal masses in young patients regressed after treatment without recurrence, supporting the recommendation that invasive procedures should be avoided unless lesions or other symptoms/signs of concern persist for > 6 months.

Publications

Tamarozzi F et al, J Trav Med, 2021. https://doi.org/10.1093/jtm/taab122

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

SchisMicrobiota. Schistosoma-associated microbiota.

- Project coordinator: University of Cambridge, Cambridge, UK.? O DITM??
- DITM P.I. Fabio Formenti
- Other institutions involved: University of Valencia, Spain. Wellcome Genome Campus, Hinxton, UK.
- Start date: 2019
- End date: Ongoing

Background and purpose

Symbiont microbial communities play important roles in animal biology and are thus considered integral components of metazoan organisms, including parasitic worms (helminths). Nevertheless, the study of helminth microbiomes has thus far been largely overlooked, and symbiotic relationships between helminths and their microbiomes have been only investigated in selected parasitic worms. Over the past decade, advances in next-generation sequencing technologies, coupled with their increased affordability, have spurred investigations of helminth-associated microbial communities aiming at enhancing current understanding of their fundamental biology and physiology, as well as of host-microbe interactions.

Methods

Using the blood fluke *Schistosoma mansoni* as a key example of parasitic worms with complex life cycles involving multiple hosts, we aim to provide an overview of protocols for sample collection and outline an example workflow to characterize worm-associated microbial communities using high-throughput sequencing technologies and bioinformatics analyses of large-scale sequence data.

Results

Protocol and example workflow to characterize worm-associated microbial communities.

Publications

Formenti F et al, Parasite Genomics, 2021. https://doi.org/10.1007/978-1-0716-1681-9_15

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

EchiSer. Serology for the diagnosis of human hepatic cystic echinococcosis.

- Project coordinator: DITM
- P.I. Francesca Tamarozzi
- Other institutions involved: University of Bern, Bern, Switzerland. Instituto de Recursos Naturales y Agrobiología de Salamanca, Spain. IRCCS San Matteo Hospital Foundation, Pavia, Italy. University of Pavia, Italy. Instituto Peruano de Parasitologia Clinica y Experimental, Lima, Peru.
- Start date: 2019
- End date: 2021

Background and purpose

Cystic echinococcosis (CE) is a neglected zoonosis caused by infection with the larval stage of the cestode *Echinococcus granulosus* sensu lato. The parasite is transmitted between canid definitive hosts and livestock, mainly sheep, as in-

termediate hosts. Humans are dead-end intermediate hosts, in whom the larval stage develops as fluid-filled cysts mainly in liver and lungs. The diagnosis of cystic echinococcosis (CE) is primarily based on imaging, while serology should be applied when imaging is inconclusive. CE cyst stage has been reported among the most important factors influencing the outcome of serodiagnosis. With this project we aimed to assess the best serologic approach as a complement for the diagnosis of hepatic echinococcosis, as well as to study the performance of a Rapid Diagnostic Test in the field in a resource-limited setting.

Methods

1. We performed a systematic review with meta-analysis on accuracy of serologic tests.

2. We did a diagnostic study on 9 commercial tests using serum specimens stored in biobank: from subjects with hepatic CE (45 "liquid" content stages, 25 "solid" content stages) and non-CE focal liver lesions (54 with "liquid" content, 11 with "solid" content).

3. We did a filed study in Peru on a rapid serologic test.

Results

1. The results of the meta-analysis confirm the presence of a clear relation between cyst stage and serology results, indicating the need to consider cyst staging when evaluating serology results.

2. In the diagnostic study, sensitivity ranged from 43 to 94% and from 31 to 87%, and specificity from 68 to 100% and from 94 to 100%, when borderline results were considered positive or negative, respectively. Best results were obtained using WB-LDBIO alone (Se 83%) or as a third test after two non-WB tests (Se 67-86%).

3. VIRapid test showed similar sensitivity (76% versus 74%) and lower specificity (79% versus 96%) than results obtained in a hospital setting. VIRapid test could help clinical decision making in resource-limited settings.

Publications

Tamarozzi F et al, PLOS Negl Trop Dis, 2021. https://doi.org/10.1371/journal.pntd.0009370

Tamarozzi F et al, Diagnostics, 2021. https://doi.org/10.3390/diagnostics11020167

Manciulli T et al, Am J Trop Med & Hygiene, 2021. https://doi.org/10.4269/ajtmh.21-0045

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

EchinReact. Accuracy of an experimental whole-blood test for detecting reactivation of echinococcal cysts

- Project coordinator: INMI Spallanzani IRCCS, Rome.
- DITM P.I. Francesca Tamarozzi
- Other institutions involved: IRCCS San Matteo Hospital Foundation, Pavia, Italy. Istituto Superiore di Sanità, Rome, Italy. University of Pavia, Italy.
- Start date: 2019
- End date: 2021

Background and purpose

Cystic echinococcosis (CE) is a complex disease for which clear understanding of clinical manifestations is needed to avoid misdiagnosis, inappropriate treatment, and severe complications. We evaluated the accuracy of a whole-blood stimulation test based on Interleukin (IL)-4 detection in response to Antigen B (AgB) of Echinococcus granulosus sensu lato to discriminate cyst viability and detect cyst reactivation in patients with hepatic CE.

Methods

Thirty patients with CE3b cysts and 37 patients with spontaneously-inactivated CE4-CE5 cysts were recruited (T0). After enrollment, 5 patients with CE3b cysts received albendazole, resulting in cyst solidification (CE4) in 4/5. Within a two-year follow-up, the whole-blood test was repeated at two time-points, in ≥14 (T1) and in ≥4 (T2) patients per group. IL-4 and a panel of other soluble factors were measured in the stimulated plasma.

Results

Baseline IL-4 levels were significantly higher in patients with CE3b compared to those with CE4 cysts. Test accuracy for CE3b diagnosis had a sensitivity of 33-60% and a specificity of 76-95%, depending on the cut-off applied. Overall, IL-4 levels did not change significantly over time in either group; however, patients within the CE3b group showed a significant decrease of IL-1ra, IL-6, IL-8, G-CSF, IFN- , IP-10, MCP-1,

MIP-1 , FGF at T1 compared to T0. Whole-blood IL-4-response to AgB is significantly higher in patients with active compared to inactive CE but apparently not modulated over time after treatment. On the contrary, the levels of IL-1ra, IL-6, IL-8, G-CSF, IFN- , IP-10, MCP-1, MIP-1 , FGF significantly decreased in active CE during follow-up.

Publications

Petrone L et al, PLOS Negl Trop Dis, 2021. https://doi.org/10.1371/journal.pntd.0009648

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

ElisHansen. ELISA test based on the phenolic glycolipid-I (PGL-I) of Mycobacterium leprae: adapted and validated to a not endemic reality.

- Project coordinator: DITM
- P.I. Silvia Stefania Longoni
- Other institutions involved: Colorado State University, United States
- Start date: 2019
- End date: 2022

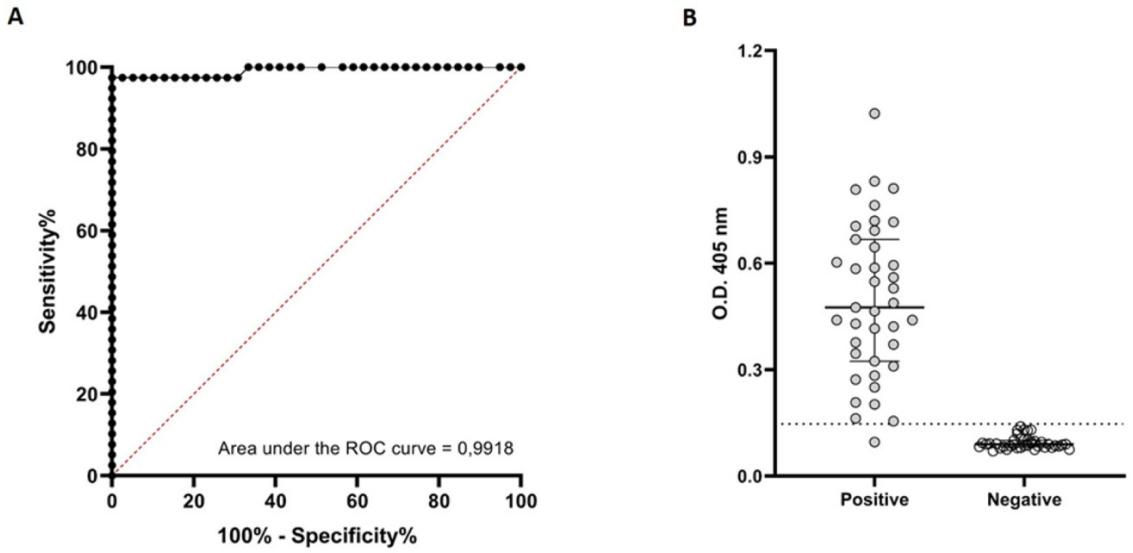
Background and purpose

Leprosy is a neglected tropical disease caused by *Mycobacterium leprae*, leading to disabilities if untreated. The ELISA based on phenolic glycolipid I (PGL-I), or its synthetic version ND-O-BSA, is almost universally positive in multibacillary leprosy and thus extensively used in endemic countries. Household contacts with a positive antibody titer have ~6-fold higher probability to develop the disease than those with a negative titer. Thus, the aim of the study was to evaluate the performance of this ELISA in the setting of a non-endemic country.

Methods

We calculate the cut-off using optimized O.D. thresholds, generated by receiver operating characteristics (ROC) curve analysis, testing 39 well-characterized sera obtained

from lepromatous leprosy patients with strongly positive ND-O-BSA ELISA titer and 39 sera from healthy non-endemic patients never exposed to M. leprae or M. tuberculosis. Indeed, we tested a second set of sera from suspected or confirmed leprosy or household contacts (SLALT group, n=50), and patients with tuberculosis (control group, n=40).



C

Cut-off value	Sensitivity % (95% CI)	Specificity % (95% CI)
0.1472	97.44 (86.82-99.87)	100 (91.03-100.0)

Diagnostic performance of ELISA based on ND-O-BSA.(A): Receiver Operating Characteristic (ROC) curves for the detection of antibodies against ND-O-BSA antigen and corresponding areas under the curve (AUC) statistics. The black dotted line shows the mean area under the curve (AUC) plot. The sensitivity and specificity values correspond to the points in the plots. (B): Antigen-specific responses of positive (anti-PGL-I seropositive leprosy patients) and negative (healthy volunteers with no suspect of contact with M. leprae) control cases. The median with interquartile range is represented by the horizontal bar while the horizontal black dotted line represent the threshold for determining a positive result (OD = 0.147) previously established by the ROC curve. (C). threshold (cut-off value) for determining a positive result. CI = 95% confidence interval.

Results

We detected 56.4% of SLALT and 22.5% of tuberculosis as positive, consistent with the literature.

Conclusion: The ELISA based on ND-O-BSA may thus be considered a good option to be used in a non-endemic area as a screening tool in at risk population usually coming to our center.

Publications

Longoni SS et al, Pathogens, 2022. https://doi.org/10.3390/pathogens11080894

Funding

Fondo Ricerca Corrente, Italian Ministry of Health.

LIST OF PUBLICATIONS

Year 2020

Research line n. 1: Global Health: Communicable and mobility-related diseases

Publication	IF	Normalized IF
Vellere I, Lagi F, Spinicci M, Mantella A, Mantengoli E, Corti G, Colao MG, **Gobbi F**, Rossolini GM, Bartoloni A, Zammarchi L. *Arbo-Score:* ***A Rapid Score for Early Identification of Patients with Imported Arbovirosis Caused by*** Dengue, Chikungunya and Zika Virus. **Microorganisms**. 2020 Nov 4;8(11):1731. doi: 10.3390/microorganisms8111731. PMID: 33158274; PMCID: PMC7716211.	4,152	3,6
Boccolini D, Menegon M, Di Luca M, Toma L, Severini F, Marucci G, D'Amato S, Caraglia A, Maraglino FP, Rezza G, Romi R, Gradoni L, Severini C; **Italian Malaria Surveillance Group**. ***Non-imported malaria in Italy: paradigmatic approaches and public health implications following an unusual cluster of cases in 2017.*** **BMC Public Health.** 2020 Jun 5;20(1):857. doi: 10.1186/s12889-020-08748-9. PMID: 32503526; PMCID: PMC7275312.	2,521	**0**
Lingscheid T, Kurth F, Stegemann MS, Clerinx J, Calleri G, Rothe C, **Angheben A, Gobbi F, Bisoffi Z,** Hamer DH, Libman M, Hatz C, Zoller T. ***Outpatient treatment of imported uncomplicated Plasmodium falciparum malaria: results from a survey among TropNet and GeoSentinel experts for tropical medicine.*** **J Travel Med.** 2020 Jul 14;27(4):taaa082. doi: 10.1093/jtm/taaa082. PMID: 32442249.	7,089	**4,8**

Gobbi F, Buonfrate D, Riccardi N, Moro L, Angheben A. ***An outbreak of blister beetle dermatitis in travellers.*** J Travel Med. 2020 Sep 26;27(6):taaa079. doi: 10.1093/jtm/taaa079. PMID: 32479609.	7,089	**3**
Dudouet P, Gautret P, Larsen CS, Díaz-Menéndez M, Trigo E, von Sonnenburg F, **Gobbi F**, Grobusch MP, Malvy D, Field V, Asgeirsson H, Souto IO, Hamer DH, Parola P, Javelle E. ***Chikungunya resurgence in the Maldives and risk for importation via tourists to Europe in 2019-2020: A GeoSentinel case series.*** Travel Med Infect Dis. 2020 Jul-Aug;36:101814. doi: 10.1016/j.tmaid.2020.101814. Epub 2020 Jun 30. PMID: 32619732; PMCID: PMC7324928.	4,589	**3**
Beltrame A, Rodari P, Mauroner L, Zanella F, **Moro L, Bertoli G**, Da Re F, Russo F, Napoletano G, **Silva R.** ***Emergence of Lyme borreliosis in the province of Verona, Northern Italy: Five-years of sentinel surveillance.*** Ticks Tick Borne Dis. 2021 Mar;12(2):101628. doi: 10.1016/j.ttbdis.2020.101628. Epub 2020 Dec 13. PMID: 33373892.	2,749	4
Lazzarini L, Barzon L, Foglia F, Manfrin V, Pacenti M, Pavan G, Rassu M, Capelli G, Montarsi F, Martini S, Zanella F, Padovan MT, Russo F, **Gobbi F.** ***First autochthonous dengue outbreak in Italy, August 2020.*** Euro Surveill. 2020 Sep;25(36):2001606. doi: 10.2807/1560-7917.ES.2020.25.36.2001606. PMID: 32914745; PMCID: PMC7502902.	6,454	**3**
Díaz-Menéndez M, Esteban ET, Ujiie M, Calleri G, Rothe C, Malvy D, Nicastri E, Bissinger AL, Grandadam M, Alpern JD, **Gobbi F**, Schlagenhauf P, Duvignaud A, Javelle E, Nakamoto T, Antinori S, Hamer DH. ***Travel-associated chikungunya acquired in Myanmar in 2019.*** Euro Surveill. 2020 Jan;25(1):1900721. doi: 10.2807/1560-7917.ES.2020.25.1.1900721. PMID: 31937394; PMCID: PMC6961262.	6,454	**3**

Pomari E, Silva R, Moro L, La Marca G, Perandin F, Verra F, **Bisoffi Z, Piubelli C**. ***Droplet Digital PCR for the Detection of Plasmodium falciparum DNA in Whole Blood and Serum: A Comparative Analysis with Other Molecular Methods.*** **Pathogens**. 2020 Jun 17;9(6):478. doi: 10.3390/pathogens9060478. PMID: 32560386; PMCID: PMC7350319.	3,018	**4**
Bisoffi Z, Bertoldi M, **Silva R, Bertoli G, Ursini T, Marocco S, Piubelli C, Pomari E, Buonfrate D, Gobbi F**. ***Dynamics of anti-malarial antibodies in non-immune patients during and after a first and unique Plasmodium falciparum malaria episode.*** **Malar J.** 2020 Jun 26;19(1):228. doi: 10.1186/s12936-020-03300-x. PMID: 32590983; PMCID: PMC7316638.	2,631	**6**
Di Ruscio M, Variola A, **Angheben A, Resimini S**, Geccherle A, Ruffo G, Barugola G. ***A Challenging Colectomy for Acute Severe Ulcerative Colitis Complicated by COVID-19.*** **Inflamm Bowel Dis.** 2020 Sep 18;26(10):e120-e122. doi: 10.1093/ibd/izaa186. PMID: 32626898; PMCID: PMC7529110.	4,261	**0**
Olivari L**, Riccardi N, Rodari P, Buonfrate D,** Diodato S, **Formenti F, Angheben A,** Salgarello M. ***Accidental diagnosis of COVID-19 pneumonia after 18F FDG PET/CT: a case series.*** **Clin Transl Imaging**. 2020 Sep 24:1-8. doi: 10.1007/s40336-020-00388-8. Epub ahead of print. PMID: 32989417; PMCID: PMC7512221.	2,506	**5**
Olivari L, **Riccardi N, Rodari P, Angheben A**, Artioli P, Salgarello M. ***COVID-19 pneumonia: increased choline uptake with 18F-choline PET/CT.*** **Eur J Nucl Med Mol Imaging**. 2020 Sep;47(10):2476-2477. doi: 10.1007/s00259-020-04870-3. Epub 2020 Jun 4. PMID: 32500168; PMCID: PMC7272208.	7,081	**3,75**
Greenaway C, Hargreaves S, Barkati S, Coyle CM, **Gobbi F,** Veizis A, Douglas P. ***COVID-19: Exposing and addressing health disparities among ethnic minorities and migrants***. **J Travel Med.** 2020 Nov 9;27(7):taaa113. doi: 10.1093/jtm/taaa113. PMID: 32706375; PMCID: PMC7454797.	7,089	**4,5**

Tilli M, Olliaro P, **Gobbi F, Bisoffi Z,** Bartoloni A, Zammarchi L. ***Neglected tropical diseases in non-endemic countries in the era of COVID-19 pandemic: the great forgotten***. **J Travel Med.** 2021 Jan 6;28(1):taaa179. doi: 10.1093/jtm/taaa179. PMID: 32970143; PMCID: PMC7543559.	7,089	**4,8**
Mantica G, **Riccardi N,** Terrone C, Gratarola A. ***Non-COVID-19 visits to emergency departments during the pandemic: the impact of fear.*** **Public Health.** 2020 Jun;183:40-41. doi: 10.1016/j.puhe.2020.04.046. Epub 2020 May 7. PMID: 32417567; PMCID: PMC7203034.	1,774	**0**
Piubelli C, Deiana M, Pomari E, Silva R, Bisoffi Z, Formenti F, Perandin F, Gobbi F, Buonfrate D. ***Overall decrease in SARS-CoV-2 viral load and reduction in clinical burden: the experience of a hospital in northern Italy.*** **Clin Microbiol Infect.** 2021 Jan;27(1):131.e1-131.e3. doi: 10.1016/j.cmi.2020.10.006. Epub 2020 Oct 12. PMID: 33059091; PMCID: PMC7548572.	7,117	**7,5**
Guerriero M, **Bisoffi Z,** Poli A, Micheletto C, Pomari C**.** ***Prevalence of asymptomatic SARS-CoV-2-positive individuals in the general population of northern Italy and evaluation of a diagnostic serological ELISA test: a cross-sectional study protocol.*** **BMJ Open**. 2020 Oct 6;10(10):e040036. doi: 10.1136/bmjopen-2020-040036. PMID: 33028562; PMCID: PMC7539547.	2,496	**5**
Deiana M, Mori A, Piubelli C, Scarso S, Favarato M, **Pomari E.** ***Assessment of the direct quantitation of SARS-CoV-2 by droplet digital PCR.*** **Sci Rep.** 2020 Oct 30;10(1):18764. doi: 10.1038/s41598-020-75958-x. PMID: 33127953; PMCID: PMC7599326.	3,998	**7,50**
Intra J, Sarto C, Beck E, **Tiberti N,** Leoni V, Brambilla P. ***Bacterial and fungal colonization of the respiratory tract in COVID-19 patients should not be neglected.*** **Am J Infect Control.** 2020 Sep;48(9):1130-1131. doi: 10.1016/j.ajic.2020.06.185. Epub 2020 Jun 25. PMID: 32593810; PMCID: PMC7315146.	2,294	**1,5**

Bisoffi Z, Pomari E, Deiana M, Piubelli C, Ronzoni N, Beltrame A, Bertoli G, Riccardi N, Perandin F, Formenti F, Gobbi F, Buonfrate D, Silva R. ***Sensitivity, Specificity and Predictive Values of Molecular and Serological Tests for COVID-19: A Longitudinal Study in Emergency Room.*** **Diagnostics (Basel).** 2020 Sep 3;10(9):669. doi: 10.3390/diagnostics10090669. PMID: 32899333; PMCID: PMC7555224.	3,11	**7,50**
Riccardi N, Villa S, Alagna R, Giacomelli A, Saderi L, Cirillo DM, Besozzi G, Sotgiu G, Codecasa L. ***Advantages and Challenges of Tailored Regimens for Drug-Resistant Tuberculosis: A StopTB Italia Look into the Future.*** **Infect Drug Resist.** 2020 Aug 11;13:2795-2800. doi: 10.2147/IDR.S257480. PMID: 32848428; PMCID: PMC7429110.	2,984	**2**
Petruccioli E, Chiacchio T, Navarra A, Vanini V, Cuzzi G, Cimaglia C, Codecasa LR, Pinnetti C, **Riccardi N,** Palmieri F, Antinori A, Goletti D. ***Effect of HIV-infection on QuantiFERON-plus accuracy in patients with active tuberculosis and latent infection.*** **J Infect.** 2020 May;80(5):536-546. doi: 10.1016/j.jinf.2020.02.009. Epub 2020 Feb 22. PMID: 32097688.	4,842	**3,6**
Requena-Méndez A, **Bisoffi Z**, Vives-Corrons JL, Gascon J, Plasència A. ***European expert network on rare communicable diseases and other rare diseases linked to mobility and globalisation focused on health care provision (EU-RaDMoG): a feasibility study***. **Orphanet J Rare Dis.** 2020 Oct 16;15(1):291. doi: 10.1186/s13023-020-01534-1. PMID: 33066818; PMCID: PMC7563907.	3,523	**2**
Villa S, **Riccardi N,** Canetti D, Alagna R, Castellotti P, Ferrarese M, Cirillo D, Barberis I, Bragazzi NL, Gazzaniga V, Ricucci V, Codecasa LR, Besozzi G, Martini M. ***From the past, a long way to future challenges for a greater control of tuberculosis.*** **Tuberculosis** (Edinb). 2020 Jul;123:101948. doi: 10.1016/j.tube.2020.101948. Epub 2020 Jun 6. PMID: 32741532.	2,576	**1,2**

Canetti D, **Riccardi N**, Martini M, Villa S, Di Biagio A, Codecasa L, Castagna A, Barberis I, Gazzaniga V, Besozzi G. ***HIV and tuberculosis: The paradox of dual illnesses and the challenges of their fighting in the history***. Tuberculosis (Edinb). 2020 May;122:101921. doi: 10.1016/j.tube.2020.101921. Epub 2020 Mar 25. PMID: 32501257.	2,576	0,00
Del Puente F**, Riccardi N,** Taramasso L, Sarteschi G, Pincino R, Di Biagio A. ***Migrants and imported disease: Trends of admission in an Italian infectious disease ward during the migration crisis of 2015-2017.*** **BMC Public Health.** 2020 May 20;20(1):738. doi: 10.1186/s12889-020-08886-0. PMID: 32434483; PMCID: PMC7238611.	2,521	**2,4**
Giacobbe DR, **Riccardi N,** Vena A, Bassetti M. ***Mould Infections of Traumatic Wounds: A Brief Narrative Review.*** **Infect Dis Ther.** 2020 Mar;9(1):1-15. doi: 10.1007/s40121-020-00284-8. Epub 2020 Feb 18. PMID: 32072492; PMCID: PMC7054562.	4,307	**3,6**
Riccardi N, Monticelli J, Antonello RM, Di Lallo G, Frezza D, Luzzati R, Di Bella S. ***Therapeutic Options for Infections due to vanB Genotype Vancomycin-Resistant Enterococci***. **Microb Drug Resist.** 2021 Apr;27(4):536-545. doi: 10.1089/mdr.2020.0171. Epub 2020 Aug 14. PMID: 32799629.	2,296	**2**
Nicolini LAP, Stoney RJ, Della Vecchia A, Grobusch M, Gautret P, Angelo KM, van Genderen PJJ, Bottieau E, Leder K, Asgeirsson H, Leung DT, Connor B, Pandey P, Toscanini F, **Gobbi F,** Castelli F, Bassetti M, Hamer DH. ***Travel-related hepatitis E: a two-decade GeoSentinel analysis.*** **J Travel Med.** 2020 Nov 9;27(7):taaa132. doi: 10.1093/jtm/taaa132. PMID: 32789467.	7,089	**3**

Research Line n. 2: Neglected Infectious and Tropical Diseases (NTD)

Publication	IF	Normalized IF
Tiberti N, Buonfrate D, Carbone C, Piro G**, Bisoffi Z, Piubelli C.** ***Systemic profile of immune factors in an elderly Italian population affected by chronic strongyloidiasis.*** **Parasit Vectors.** 2020 Oct 15;13(1):515. doi: 10.1186/s13071-020-04391-w. PMID: 33059754; PMCID: PMC7559927.	2,824	**6**
Wikman-Jorgensen PE, Llenas-Garcia J, Shedrawy J, Gascon J, Muñoz J, **Bisoffi Z,** Requena-Mendez A. ***Cost-effectiveness of different strategies for screening and treatment of Strongyloides stercoralis in migrants from endemic countries to the European Union.*** **BMJ Glob Health.** 2020 May;5(5):e002321. doi: 10.1136/bmjgh-2020-002321. PMID: 32461226; PMCID: PMC7254101.	4,28	**3,6**
Navarro M, Camprubí D, Requena-Méndez A, **Buonfrate D**, Giorli G, Kamgno J, Gardon J, Boussinesq M, Muñoz J, Krolewiecki A. ***Safety of high-dose ivermectin: a systematic review and meta-analysis.*** **J Antimicrob Chemother.** 2020 Apr 1;75(4):827-834. doi: 10.1093/jac/dkz524. PMID: 31960060.	5,439	**3,6**
Zammarchi L, Tilli M, Botta A, **Buonfrate D,** Bartoloni A, Boccalini S. ***Strategies for management of strongyloidiasis in migrants from Sub-Saharan Africa recently arrived in Italy: A cost-effectiveness analysis.*** **Travel Med Infect Dis**. 2020 Jul-Aug;36:101561. doi: 10.1016/j.tmaid.2020.101561. Epub 2020 Jan 23. PMID: 31982632.	4,589	**3,6**
Buonfrate D, Bisanzio D, Giorli G, Odermatt P, Fürst T, Greenaway C, French M, Reithinger R, **Gobbi F,** Montresor A, **Bisoffi Z.** ***The Global Prevalence of Strongyloides stercoralis Infection***. **Pathogens.** 2020 Jun 13;9(6):468. doi: 10.3390/pathogens9060468. PMID: 32545787; PMCID: PMC7349647.	3,018	**4**

Farthing M, Albonico M, **Bisoffi Z,** Bundy D, **Buonfrate D,** Chiodini P, Katelaris P, Kelly P, Savioli L, Mair AL. ***World Gastroenterology Organisation Global Guidelines: Management of Strongyloidiasis February 2018-Compact Version>.*** **J Clin Gastroenterol.** 2020 Oct;54(9):747-757. doi: 10.1097/MCG.0000000000001369. PMID: 32890112.	2,973	**1,6**
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Tamarozzi F, Horton J, Muhtarov M, Ramharter M, Siles-Lucas M, Gruener B, Vuitton DA, Bresson-Hadni S, Manciulli T, Brunetti E. ***A case for adoption of continuous albendazole treatment regimen for human echinococcal infections.*** **PLoS Negl Trop Dis**. 2020 Sep 17;14(9):e0008566. doi: 10.1371/journal.pntd.0008566. PMID: 32941434; PMCID: PMC7498015.	3,885	**0,00**
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Total Impact Factor 253,95

Total Normalized Impact Factor 220,40

Year 2021

Research line n. 1: Global Health: Communicable and mobility-related diseases

Publication	IF	Normalized IF
Bertoli G, Mazzi C, Ronzoni N, Silva R, Spinicci M, Pozzi M, Sponga P, Aiello A, **Ursini T,** Bartoloni A, Olliaro P, **Bisoffi Z, Buonfrate D. C-Reactive Protein for the Early Assessment of Non-Malarial Febrile Patients: A Retrospective Diagnostic Study. Diagnostics (Basel).** 2021 Sep 20;11(9):1728. doi: 10.3390/diagnostics11091728. PMID: 34574070; PMCID: PMC8469932.	3,71	**6,00**
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Deledda G, **Riccardi N,** Gori S, Poli S, Giansante M, Geccherle E, **Mazzi C, Silva R,** Desantis N, Giovannetti AM, Solari A, Confalonieri P, Grazzi L, Sarcletti E, Biffa G, Biagio AD, Sestito C, Keim R, Gangi Hermis AMRD, Mazzoldi M, Failo A, Scaglione A, Faldetta N, Dorangricchia P, Moschetto M, Soto Parra HJ, Faietti J, Profio AD, Rusconi S, Giacomelli A, Marchioretto F, Alongi F, Marchetta A, Molon G**, Bisoffi Z, Angheben A. The Impact of the SARS-CoV-2 Outbreak on the Psychological Flexibility and Behaviour of Cancelling Medical Appointments of Italian Patients with Pre-Existing Medical Condition: The "ImpACT-COVID-19 for Patients" Multi-Centre Observational Study. Int J Environ Res Public Health.** 2021 Jan 5;18(1):340. doi: 10.3390/ijerph18010340. PMID: 33466374; PMCID: PMC7794735.	3,39	**4,80**

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Gobbi F, Buonfrate D, Silva R, Martini D, **Bisoffi Z, Piubelli C**, Riccetti S, Sinigaglia A, Barzon L. **Antibody response in individuals infected with SARS-CoV-2 early after the first dose of the BNT162b2 mRNA vaccine. J Infect.** 2022 Jan;84(1):94-118. doi: 10.1016/j.jinf.2021.08.008. Epub 2021 Aug 8. PMID: 34371075; PMCID: PMC8349413.	6,07	**3,00**

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Musicò A, Frigerio R, Mussida A, Barzon L, Sinigaglia A, Riccetti S, **Gobbi F, Piubelli C**, Bergamaschi G, Chiari M, Gori A, Cretich M. **SARS-CoV-2 Epitope Mapping on Microarrays Highlights Strong Immune-Response to N Protein Region. Vaccines (Basel).** 2021 Jan 11;9(1):35. doi: 10.3390/vaccines9010035. PMID: 33440622; PMCID: PMC7827214.	4,42	**3,20**
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Riccardi N, Villa S, Giacomelli A, Diaw MM, Ndiaye M, Gning L, Robbiano M, Alagna R, Saderi L, Biagio AD, Bassetti M, Cirillo DM, Sotgiu G, Codecasa LR, Sarr M, Besozzi G. **Tuberculosis treatment outcomes in a rural area of Senegal: a decade of experience from 2010 to 2019 by StopTB Italia. Future Microbiol.** 2021 Apr;16:399-407. doi: 10.2217/fmb-2020-0238. Epub 2021 Apr 13. PMID: 33847143.	3,17	**2,00**
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Research line n. 2: Neglected Infectious and Tropical Diseases (NTD)

Publication	IF	Normalized IF
Buonfrate D, Fittipaldo A, Vlieghe E, Bottieau E. **Clinical and laboratory features of Strongyloides stercoralis infection at diagnosis and after treatment: a systematic review and meta-analysis. Clin Microbiol Infect.** 2021 Nov;27(11):1621-1628. doi: 10.1016/j.cmi.2021.07.016. Epub 2021 Jul 26. PMID: 34325063.	8,07	**6,00**
Buonfrate D, Zammarchi L, **Bisoffi Z,** Montresor A, Boccalini S. **Control programs for strongyloidiasis in areas of high endemicity: an economic analysis of different approaches. Infect Dis Poverty.** 2021 May 25;10(1):76. doi: 10.1186/s40249-021-00858-9. PMID: 34030741; PMCID: PMC8147038.	4,39	**6,00**

Bisoffi Z, Buonfrate D. Moxidectin: an ally to ivermectin for treating Strongyloides stercoralis? Lancet Infect Dis. 2021 Aug;21(8):1060-1061. doi: 10.1016/S1473-3099(20)30718-0. Epub 2021 Mar 30. PMID: 33798488.	25,07	**0,00**
Bisanzio D, Montresor A, French M, Reithinger R, **Rodari P, Bisoffi Z, Buonfrate D. Preventive chemotherapy for the control of strongyloidiasis in school-age children: Estimating the ivermectin need. PLoS Negl Trop Dis.** 2021 Apr 15;15(4):e0009314. doi: 10.1371/journal.pntd.0009314. PMID: 33857134; PMCID: PMC8078808.	4,41	**6,00**
Tamarozzi F, Longoni SS, Mazzi C, Pettene S, Montresor A, Mahanty S, **Bisoffi Z, Buonfrate D. Diagnostic accuracy of a novel enzyme-linked immunoassay for the detection of IgG and IgG4 against Strongyloides stercoralis based on the recombinant antigens NIE/SsIR. Parasit Vectors.** 2021 Aug 18;14(1):412. doi: 10.1186/s13071-021-04916-x. PMID: 34407876; PMCID: PMC8375122.	3,88	**6,00**
Buonfrate D, Marrone R, Silva R, Mirisola C, **Ragusa A, Mistretta M, Perandin F, Bisoffi Z. Prevalence of Strongyloidiasis in a Cohort of Migrants in Italy and Accuracy of a Novel ELISA Assay for S. stercoralis Infection, a Cross-Sectional Study. Microorganisms.** 2021 Feb 15;9(2):401. doi: 10.3390/microorganisms9020401. PMID: 33671980; PMCID: PMC7919371.	4,13	**4,00**
Salvador F, Lucas-Dato A, Roure S, Arsuaga M, Pérez-Jacoiste A, García-Rodríguez M, Pérez-Molina JA, **Buonfrate D,** Saugar JM, Molina I. **Effectiveness and Safety of a Single-Dose Ivermectin Treatment for Uncomplicated Strongyloidiasis in Immunosuppressed Patients (ImmunoStrong Study): The Study Protocol. Pathogens.** 2021 Jun 27;10(7):812. doi: 10.3390/pathogens10070812. PMID: 34199000; PMCID: PMC8308528.	3,49	**2,00**
Cassini R, Canali M, **Tamarozzi F, Angheben A**, Capelli G, **Gobbi F,** Legnardi M, Brichese M, Napoletano G, Cestaro F, Casulli A, Drigo M, Aragrande M. **A One-Health evaluation of the burden of cystic echinococcosis and its prevention costs: Case study from a hypo-endemic area in Italy. One Health.** 2021 Aug 30;13:100320. doi: 10.1016/j.onehlt.2021.100320. PMID: 34504939; PMCID: PMC8413884.	3,80	**4,00**

Lightowlers MW, Gasser RB, Hemphill A, Romig T, **Tamarozzi F,** Deplazes P, Torgerson PR, Garcia HH, Kern P. **Advances in the treatment, diagnosis, control and scientific understanding of taeniid cestode parasite infections over the past 50 years. Int J Parasitol.** 2021 Dec;51(13-14):1167-1192. doi: 10.1016/j.ijpara.2021.10.003. Epub 2021 Oct 30. PMID: 34757089.	3,98	**3,60**
Arsuaga M, Díaz-Menéndez M, **Gobbi FG. Autochthonous schistosomiasis in Europe: A silent threat. Travel Med Infect Dis.** 2022 Jan-Feb;45:102244. doi: 10.1016/j.tmaid.2021.102244. Epub 2021 Dec 21. PMID: 34942375.	6,21	**0,00**
Mendes, F.S.N.S., Perez-Molina, J.A., **Angheben, A.,** Meymandi, S.K., Sosa-Estani, S., Molina, I. **Critical analysis of chagas disease treatment in different countries (2021) Memorias do Instituto Oswaldo Cruz**, 116 (1), art. no. e210034,	2,74	**2,40**
Tamarozzi F, Fittipaldo VA, Orth HM, Richter J, Bu**onfrate D, Riccardi N, Gobbi FG. Diagnosis and clinical management of hepatosplenic schistosomiasis: A scoping review of the literature. PLoS Negl Trop Dis.** 2021 Mar 25;15(3):e0009191. doi: 10.1371/journal.pntd.0009191. PMID: 33764979; PMCID: PMC7993612.	4,41	**6,00**
Umbrello G, Pinzani R, Bandera A, **Formenti F**, Zavarise G, Arghittu M, Girelli D, Maraschini A, Muscatello A, Marchisio P, Bosis S. **Hookworm infection in infants: a case report and review of literature. Ital J Pediatr.** 2021 Feb 9;47(1):26. doi: 10.1186/s13052-021-00981-1. PMID: 33563313; PMCID: PMC7871578.	2,64	**1,20**
Costa C, Ferrari A, Binazzi R, **Beltrame A**, Tacconi D, **Moro L**, Edouard S, Parola P, **Buonfrate D, Gobbi F. Imported scrub typhus in Europe: Report of three cases and a literature review. Travel Med Infect Dis.** 2021 Jul-Aug;42:102062. doi: 10.1016/j.tmaid.2021.102062. Epub 2021 Apr 17. PMID: 33862243.	6,21	**6,00**
Vieri MK, Mandro M, **Cardellino CS**, **Orza P, Ronzoni N,** Siewe Fodjo JN, Hotterbeekx A, Colebunders R. **Potential Parasitic Causes of Epilepsy in an Onchocerciasis Endemic Area in the Ituri Province, Democratic Republic of Congo. Pathogens.** 2021 Mar 18;10(3):359. doi: 10.3390/pathogens10030359. PMID: 33803565; PMCID: PMC8002919.	3,49	**4,00**

Riccardi N, Giacomelli A, Antonello RM, **Gobbi F, Angheben A. Rabies in Europe: An epidemiological and clinical update. Eur J Intern Med.** 2021 Jun;88:15-20. doi: 10.1016/j.ejim.2021.04.010. Epub 2021 Apr 29. PMID: 33934971.	4,62	6,00
Nordmann T, Schlabe S, Feldt T, **Gobbi F,** Krieg A, Bode JG, Fuchs A, Kraef C, Praktiknjo M, Trebicka J, Ramharter M, Addo MM, Strassburg C, Lohse AW, Luedde T, Schmiedel S, Orth HM. **TIPS and splenorenal shunt for complications of portal hypertension in chronic hepatosplenic schistosomiasis-A case series and review of the literature. PLoS Negl Trop Dis.** 2021 Dec 21;15(12):e0010065. doi: 10.1371/journal.pntd.0010065. PMID: 34932562; PMCID: PMC8726476.	4,41	**3,60**
Casulli A, **Tamarozzi F. Tracing the source of infection of cystic and alveolar echinococcosis, neglected parasitic infections with long latency: The shaky road of "evidence" gathering. PLoS Negl Trop Dis.** 2021 Jan 21;15(1):e0009009. doi: 10.1371/journal.pntd.0009009. PMID: 33476336; PMCID: PMC7819598.	4,41	**0,00**
Shams S, Niloofar Rezaie, Beltrame A, **Moro L, Piubelli C**, Amiri FB, Esmaeili S. **Tropheryma whipplei intestinal colonization in immunocompromised children in Iran: a preliminary study. Future Microbiol.** 2021 Oct;16:1161-1166. doi: 10.2217/fmb-2021-0091. Epub 2021 Oct 7. PMID: 34615382.	3,17	**2,00**
Petrone L, **Tamarozzi F**, Vola A, Gomez Morales MA, Ludovisi A, Najafi Fard S, Mariconti M, Brunetti E, Goletti D. **Accuracy of an experimental whole-blood test for detecting reactivation of echinococcal cysts. PLoS Negl Trop Dis.** 2021 Aug 20;15(8):e0009648. doi: 10.1371/journal.pntd.0009648. PMID: 34415898; PMCID: PMC8378729.	4,41	**6,00**
Tamarozzi F, Longoni SS, Vola A**, Degani M, Tais S, Rizzi E, Prato M, Scarso S, Silva R**, Brunetti E, **Bisoffi Z, Perandin F. Evaluation of Nine Commercial Serological Tests for the Diagnosis of Human Hepatic Cyst Echinococcosis and the Differential Diagnosis with Other Focal Liver Lesions: A Diagnostic Accuracy Study. Diagnostics (Basel).** 2021 Jan 25;11(2):167. doi: 10.3390/diagnostics11020167. PMID: 33503986; PMCID: PMC7911993.	3,71	**6,00**

Tamarozzi F, Ursini T, Hoekstra PT, **Silva R,** Costa C, **Gobbi F, Monteiro GB, Motta L,** van Dam GJ, Corstjens PL, van Lieshout L, **Buonfrate D. Evaluation of microscopy, serology, circulating anodic antigen (CAA), and eosinophil counts for the follow-up of migrants with chronic schistosomiasis: a prospective cohort study**. **Parasit Vectors.** 2021 Mar 9;14(1):149. doi: 10.1186/s13071-021-04655-z. PMID: 33750443; PMCID: PMC7941883.	3,88	**6,00**
Manciulli T, Enríquez-Laurente R, **Tamarozzi F,** Lissandrin R, Elizalde M, Sedano C, Bardales K, Vola A, De Silvestri A, Tinelli C, Brunetti E, Santivanez S, Mariconti M. **Field Performance of a Rapid Diagnostic Test for the Serodiagnosis of Abdominal Cystic Echinococcosis in the Peruvian Highlands.** **Am J Trop Med Hyg**. 2021 May 24;105(1):181-187. doi: 10.4269/ajtmh.21-0045. PMID: 34029208; PMCID: PMC8274789.	2,35	**2,40**
Longoni SS, Tiberti N, Bisoffi Z, Piubelli C. Monoclonal Antibodies for Protozoan Infections: A Future Reality or a Utopic Idea? Front Med (Lausanne). 2021 Oct 12;8:745665. doi: 10.3389/fmed.2021.745665. PMID: 34712683; PMCID: PMC8545981.	5,09	**6,00**
Formenti F, Tang TT, **Tamarozzi F, Silva R, La Marca G, Pajola B, Piubelli C, Perandin F,** Rubio JM, Escolar EM, **Bisoffi Z, Gobbi F. Preliminary comparison between an in-house real-time PCR vs microscopy for the diagnosis of Loa loa and Mansonella perstans. Acta Trop.** 2021 Apr;216:105838. doi: 10.1016/j.actatropica.2021.105838. Epub 2021 Jan 21. PMID: 33484727.	3,11	**6,00**
Longoni SS, Piubelli C, Perandin F, Rizzi E, Luchetta N, Degani M, Tais S, Mori A, Bisoffi Z. Preliminary evaluation of a new Schistosoma Immunochromatographic Test. Acta Trop. 2021 Jul;219:105893. doi: 10.1016/j.actatropica.2021.105893. Epub 2021 Apr 16. PMID: 33872586.	3,11	**6,00**
Tamarozzi F, Ursini T, Ronzoni N, Badona Monteiro G, Gobbi FG, Angheben A, Richter J, **Buonfrate D, Bisoffi Z. Prospective cohort study using ultrasonography of Schistosoma haematobium-infected migrants. J Travel Med.** 2021 Aug 27;28(6):taab122. doi: 10.1093/jtm/taab122. PMID: 34369560.	8,49	**6,00**

Tamarozzi F, Silva R, Fittipaldo VA, Buonfrate D, Gottstein B, Siles-Lucas M. **Serology for the diagnosis of human hepatic cystic echinococcosis and its relation with cyst staging: A systematic review of the literature with meta-analysis. PLoS Negl Trop Dis.** 2021 Apr 28;15(4):e0009370. doi: 10.1371/journal.pntd.0009370. PMID: 33909640; PMCID: PMC8081258.	4,41	**6,00**

Total Impact Factor: 349,94

Total Normalized Impact Factor: 242,76

Year 2022

Research line n. 1: Global Health: Communicable and mobility-related diseases

Publication	IF	Normalized IF
Francesca Tamarozzi, Paola Rodari, Joaquín Salas-Coronas, Emmanuel Bottieau, Fernando Salvador, Manuel Jesús Soriano-Pérez, María Isabel Cabeza-Barrera, Marjan Van Esbroeck, Begoña Treviño, **Dora Buonfrate, Federico G Gobbi. A large case series of travel-related Mansonella perstans (vector-borne filarial nematode): a TropNet study in Europe. Journal of Travel Medicine.** 2022 Nov 4;29(7):taac048. doi: 10.1093/jtm/taac048.	39,194	**35**
Balogun O, Brown A, Angelo DO KM, Hochberg NS, Barnett ED, Nicolini LA, Asgeirsson H, Grobusch MP, Leder K, Salvador F, Chen L, Odolini S, Díaz-Menéndez M, **Gobbi F**, Connor BA, Libman M, Hamer DH. **Acute hepatitis a in international Travelers: A GeoSentinel analysis, 2008-2020. Journal of Travel Medicine** 2022 Mar 21;29(2):taac013. doi: 10.1093/jtm/taac013.	39,194	0

Buonfrate. Alternative treatment strategies for trichuriasis. Lancet Infectious Diseases. 2023 Mar;23(3):266-267. doi: 10.1016/S1473-3099(22)00653-3. Epub 2022 Oct 28.	71,421	**28**
ISARIC Clinical Characterisation Group. An international observational study to assess the impact of the Omicron variant emergence on the clinical epidemiology of COVID-19 in hospitalised patients. ELife 2022 Oct 5;11:e80556. doi: 10.7554/eLife.80556.	8,713	**3,6**
Anna Beltrame 1, Pedro Salguero 2, Emanuela Rossi 3, Ana Conesa 4 5, **Lucia Moro 1**, Laura Rachele Bettini 6, **Eleonora Rizzi** 1, Mariella D'Angió 6, **Michela Deiana 1, Chiara Piubelli 1,** Paola Rebora 3, Silvia Duranti 1, Paolo Bonfanti 7 8, Ilaria Capua 9, Sonia Tarazona 2, Maria Grazia Valsecchi 3. **Association Between Sex Hormone Levels and Clinical Outcomes in Patients With COVID-19 Admitted to Hospital: An Observational, Retrospective, Cohort Study.** Frontiers in Immunology. 2022 Jan 27;13:834851. doi: 10.3389/fimmu.2022.834851. eCollection 2022.	8,787	**6**
Maxim Van Herreweghe, Annelies Breynaert, Tess De Bruyne, Corneliu Petru Popescu, Simin-Aysel Florescu, Yaniv Lustig, Eli Schwartz, **Federico Gobbi**, Nina Hermans, Ralph Huits. **Can biomarkers of oxidative stress in serum predict disease severity in West Nile virus infection? A pilot study.** Tropical Medicine and Infectious Disease. 2022 Aug 24;7(9):207. doi: 10.3390/tropicalmed7090207.	3,711	**0**

Alessandra Giannella, Silvia Riccetti , Alessandro Sinigaglia, **Chiara Piubelli, Elisa Razzaboni**, Piero Di Battista, Matteo Agostini, Emanuela Dal Molin, Riccardo Manganelli, **Federico Gobbi**, Giulio Ceolotto, Luisa Barzon. **Circulating microRNA signatures associated with disease severity and outcome in COVID-19 patients. Frontiers in Immunology.** 2022 Aug 11;13:968991. doi: 10.3389/fimmu.2022.968991. eCollection 2022.	8,786	**6**
G Ciusa, F Guida Marascia, R Virruso, **A Angheben**, G Guaraldi, A Cascio. **Clinical recrudescence of chronic untreated P. malariae infection after BNT162b2 CoVID-19 vaccine. IDCases** 2022;27:e01456. doi: 10.1016/j.idcr.2022.e01456. Epub 2022 Feb 19.	NO IF	-
Evangelos J Giamarellos-Bourboulis 1 2, Garyfallia Poulakou 3, Aline de Nooijer 4, Haralampos Milionis 5, Simeon Metallidis 6, Michalis Ploumidis 7, Pinelopi Grigoropoulou 8, Aggeliki Rapti 9, Francesco Vladimiro Segala 10, Evangelos Balis 11, Efthymia Giannitsioti 12, **Paola Rodari 13**, Ilias Kainis 14, Zoi Alexiou 15, Emanuele Focà 16, Brollo Lucio 17, Nikoletta Rovina 18, Laura Scorzolini 19, Maria Dafni 20, Sofia Ioannou 21, Alessandro Tomelleri 22, Katerina Dimakou 23, Glykeria Tzatzagou 24, Maria Chini 25, Matteo Bassetti 26, Christina Trakatelli 27, George Tsoukalas 28, Carlo Selmi 29, Charilaos Samaras 30, Maria Saridaki 31, Athina Pyrpasopoulou 32, Elisabeth Kaldara 33, Ilias Papanikolaou 34, Aikaterini Argyraki 35, Karolina Akinosoglou 36, Marina Koupetori 37, Periklis Panagopoulos 38, George N Dalekos 39, Mihai G Netea 4 40. **Development and validation of SCOPE score: A clinical score to predict COVID-19 pneumonia progression to severe respiratory failure. Cell Reports Medicine** 2022 Feb 25;3(3):100560. doi: 10.1016/j.xcrm.2022.100560. eCollection 2022 Mar 15.	16,988	**10,193**
Gabriel Siracusano 1, Alessandra Ruggiero 2, **Zeno Bisoffi 3 4, Chiara Piubelli 3,** Luca Dalle Carbonare 5, Maria Teresa Valenti 5, Martin Mayora-Neto 6, Nigel Temperton 6, Lucia Lopalco 7, Donato Zipeto. **Different decay of antibody response and VOC sensitivity in naïve and previously infected subjects at 15 weeks following vaccination with BNT162b2. Journal of translational medicine.** 2022 Jan 8;20(1):22. doi: 10.1186/s12967-021-03208-3.	8,448	**4,8**

Saleh Aljadeeah 1, Joris Michielsen 2, Raffaella Ravinetto 2, Sally Hargreaves 3, Veronika J Wirtz 4, Oliver Razum 5, **Federico Gobbi 6**, Karina Kielmann. **Facilitating access to medicines and continuity of care for Ukrainian refugees: exceptional response or the promise of more inclusive healthcare for all migrants?** BMJ Global Health 2022 Aug;7(8):e010327. doi: 10.1136/bmjgh-2022-010327.	8,061	**0**
Dora Buonfrate, Fabio Chesini, Davide Martini, Maria Carla Roncaglioni, Maria Luisa Ojeda Fernandez, Maria Francesca, Alvisi, Irene De Simone, Eliana Rulli, Alessandro Nobili, Giacomo Casalini, Spinello Antinori, Marco Gobb, Caterina Campoli, **Michela Deiana, Elena Pomari,** Gianluigi Lunardi, Roberto Tessari, **Zeno Bisoffi. High dose ivermectin for the early treatment of COVID-19 (COVER study): a randomised, double-blind, multicentre, phase II, dose-finding, proof of concept clinical trial.** International Journal of Antimicrobial Agents. 2022 Feb;59(2):106516. doi: 10.1016/j.ijantimicag.2021.106516. Epub 2022 Jan 6.	15,441	**15,441**
Dora Buonfrate , Eliana Rulli **, Zeno Bisoffi. In reply to: Viral load reduction and high dose Ivermectin in early treatment: a reappraisal.** International Journal of Antimicrobial Agents. 2022 May; 59(5): 106576. doi: 10.1016/j.ijantimicag.2022.106576. Epub 2022 Mar 20.	15,441	**0**
Ambra Laura Nicolini, PhD, **Francesca Tamarozzi, PhD*, Elena Pomari, PhD, Manuela Mistretta, BSc**, Marco Camera, MD, Chiara Sepulcri, MD, Matteo Bassetti, MD, **Federico G Gobbi. Loiasis from where you don't expect it: an illustrative case of misled diagnosis.** Journal of Travel Medicine 2022 Nov 4;29(7):taac060. doi: 10.1093/jtm/taac060.	39,194	**21**
Maria Rosaria Rosaria Capobianchi, Antonino Di Caro, **Chiara Piubelli, Zeno Bisoffi, Antonio Mori and Concetta Castilletti. Monkeypox 2022 outbreak in non-endemic countries: open questions relevant for public health, nonpharmacological intervention and literature review.** Frontiers in Cellular and Infection Microbiology 2022 Sep 20;12:1005955. doi: 10.3389/fcimb.2022.1005955. eCollection 2022.	6,073	**6**

Capobianchi M, Castilletti C. **Polio is back? The risk of poliomyelitis recurrence globally, and the legacy of SARS-CoV-2 pandemic**. Clinical Microbiology and Infection 2023 Apr;29(4):414-416. doi: 10.1016/j.cmi.2022.12.005. Epub 2022 Dec 8.	13,31	**7,986**
Luisa Barzon 1 2, Monia Pacenti 2, Fabrizio Montarsi 3, Diletta Fornasiero 3, Federica Gobbo 3, Erika Quaranta 3, Isabella Monne 3, Alice Fusaro 3, Andrea Volpe 1, Alessandro Sinigaglia 1, Silvia Riccetti 1, Emanuela Dal Molin 1, Sorsha Satto 2, Vittoria Lisi 2, **Federico Gobbi 4**, Silvia Galante 5, Giuseppe Feltrin 6, Valerio Valeriano 7, Laura Favero 8, Francesca Russo 8, Matteo Mazzucato 3, Alessio Bortolami 3, Paolo Mulatti 3, Calogero Terregino 3, Gioia Capelli. **Rapid spread of a new West Nile virus lineage 1 associated with increased risk of neuroinvasive disease during a large outbreak in northern Italy, 2022: One Health analysis.** Journal of Travel Medicine 2022 Nov 4;taac125. doi: 10.1093/jtm/taac125. Online ahead of print.	39,194	**0**
Davide Treggiari, Chiara Piubelli, Fabio Formenti, Ronaldo Silva, **Francesca Perandin. Resurgence of respiratory virus after relaxation of COVID-19 containment measures. A Real-World data study from a regional hospital of Italy.** International Journal of Microbiology. 2022 Nov 25;2022:4915678. doi: 10.1155/2022/4915678. eCollection 2022.	NO IF	-
Bianchini E, Rossignolo F, Perfranceschi M, Cazzin C, Silva R, **Formenti F, Perandin F,** Griffante C, Remelli R, Padovani M, **Scarso S, Leonardi M, Piubelli C. RNA extraction alternative method for SARS-CoV-2 molecular diagnosis.** Annals of Clinical & Laboratory Science 2022 Jul;52(4):677-683.	1,18	**1**
Alessandra Ruggiero, **Chiara Piubelli**, Lucia Calciano, Simone Accordini, Maria Teresa Valenti, Luca Dalle Carbonare, Gabriel Siracusano, Nigel Temperton, **Natalia Tiberti, Silvia Stefania Longoni,** Massimo Pizzato, Silvia Accordini, A.M.S.L.V. group; Tobia Fantoni, Lucia Lopalco, Alberto Beretta, **Zeno Bisoffi,** Donato Zipeto. **SARS-CoV-2 vaccination elicits unconventional IgM specific responses in naïve and previously COVID-19-infected individuals.** EbioMedicine 2022 Mar;77:103888. doi: 10.1016/j.ebiom.2022.103888. Epub 2022 Feb 20.	11,205	11,205

Maestri, Simone; Grosso, Valentina; Alfano, Massimiliano; Lavezzari, Denise; **Piubelli, Chiara; Bisoffi, Zeno;** Rossato, Marzia; Delledonne, Massimo. **STArS (STrain-Amplicon-Seq), a targeted Nanopore sequencing workflow for SARS-CoV-2 diagnostics and genotyping.** Biology Methods & Protocols 2022 Aug 25;7(1):bpac020. doi: 10.1093/biomethods/bpac020. eCollection 2022.	NO IF	-
Niccolò Riccardi, Roberta Maria Antonello, Andrea Giacomelli, Laura Saderi, Diana Canetti, Carlo Pallotto, Fulvia Mazzaferri, Anna Maria Degli Antoni, Chiara Cardellino, Ilaria Motta, Andrea Calcagno, Marco Falcone, Michele Trezzi, Agnese Comelli, Renato Pascale, Marco Merli, Francesca Binda, **Andrea Angheben,** Giovanni Sotgiu, **Federico Gobbi,** Silvia Nozza. **The challenge of infectious diseases consultations in the emergency department: an Italian nationwide survey.** New Microbiologica. 2022 Dec;45(4):260-268. Epub 2022 Oct 3.	1,383	**0,8**
Gianluca Piovan, Luca Farinelli, Daniele Screpis, **Stefania Marocco, Leonardo Motta,** Giuseppe Palazzolo, Simone Natali, Claudio Zorzi. **The role of antibiotic calcium sulfate beads in acute periprosthetic knee infection: a retrospective cohort study.** Arthroplasty. 2022 Sep 6;4(1):42. doi: 10.1186/s42836-022-00139-2.	NO IF	-
Richard Bradbury, Sarah Sapp, Idzi Potters, Blaine Mathison, John Frean Bobbi Pritt, Harsha Sheorey, **Francesca Tamarozzi,** Marc Roger Couturier, Peter Chiodini. **Where Have all the Morphological Parasitologists Gone?** Journal of Clinical Microbiology. 2022 Nov 16;60(11):e0098622. doi: 10.1128/jcm.00986-22. Epub 2022 Oct 31.	11,677	**7,0062**

Research line n. 2: Neglected Infectious and Tropical Diseases (NTD)

Publication	IF	Normalized IF
Lissandrin, Raffaella; Vola, Ambra; Filice, Carlo; Manciulli, Tommaso; Tamarozzi, Francesca; brunetti, enrico. **Conservative management of echinococcal cysts in pregnant women. Single center experience in Pavia, Italy.** American Journal Of Tropical Medicine And Hygiene 2022 Apr 11;106(6):1684-1687. doi: 10.4269/ajtmh.21-0612.	3,707	**2,4**
Dora Buonfrate, Paola Rodari, Beatrice Barda, Wendy Page, Lloyd Einsiedel, Matthew Watts. **Current pharmacotherapeutic strategies for Strongyloidiasis and the complications in its treatment.** Expert Opinion On Pharmacotherapy 2022 Oct;23(14):1617-1628. doi: 10.1080/14656566.2022.2114829. Epub 2022 Aug 24.	4,103	**4**
Francesca Tamarozzi1*, Tito Kibona2, William A. de Glanville3, Tauta Mappi2, Elly Adonikamu4, Anande Salewi4, Kennedy Misso4, Venance Maro4,5, Adriano Casulli 6, Azzurra Santoro6, Federica Santolamazza6, Blandina T M mbaga4,5, Sarah Cleaveland3. **Cystic echinococcosis in northern Tanzania: a pilot study in Maasai livestock- keeping communities.** Parasites & Vectors. 2022 Oct 28;15(1):396. doi: 10.1186/s13071-022-05518-x.	4,052	**6**
Silvia Stefania Longoni, Anna Beltrame, **Marco Prato,** John Stewart Spencer, Nicolo Bergamaschi, Andrea Clapasson, Aurora Parodi, **Chiara Piubelli and Francesca Perandin. ELISA Test Based on the Phenolic Glycolipid-I (PGL-I) of Mycobacterium leprae: A Reality of a Laboratory from a Non-Endemic Country.** Pathogens 2022 Aug 9;11(8):894. doi: 10.3390/pathogens11080894.	4,531	**4**

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