



Penta

Child Health Research

Annual Report **2018**



Letter from the President

The Penta Foundation was established in 2004 to bring together a research network of paediatricians and clinicians to join forces and find answers and solutions to the most critical issues that HIV/AIDS posed to child health everywhere in the world.

Over time, we have established a **global independent scientific network** dedicated to paediatric research, that today encompasses more than 110 clinical sites in 31 Countries. Branching out from our initial focus on HIV, in recent years we have started investigating other infectious diseases affecting children: hepatitis, tuberculosis, Zika virus and other arboviruses, bacterial and fungal infection and antimicrobial resistance.

The ideas, ambition and passion that have been there since the outset are still burning strong. Almost 30 years since its foundation, Penta is today one of the most prominent scientific organizations **dedicated to paediatric research**. We strive to work independently, transparently and collaboratively because sharing is a value, a method and an end for us.

2018 was a pivotal year for us. We launched c4c (connect4children), an ambitious project to change the landscape of Paediatric clinical research in Europe and facilitate the development of new drugs and other therapies for children.

In terms of partnerships, 2018 saw Penta and the Global Accelerator for Paediatric Formulations (GAP-f), working together to accelerate the development, approval and introduction of new paediatric formulations. We embarked upon several key studies in collaboration with the Global Antibiotic Research & Development Partnership (GARDP) to tackle antimicrobial resistance in children and to accelerate paediatric development of antibiotic treatments. Moreover, we established an important partnership with the Joint Clinical Research Centre (JCRC) in Uganda, thereby strengthening our efforts in new research fields such as communicable and non-communicable diseases, and antimicrobial resistance.

With regard to our strategic clinical trials, we achieved our recruitment target in Odyssey, a study on a dolutegravir-based antiretroviral therapy. We are on track with patient enrolments in SMILE, another key study exploring novel antiretroviral strategies in children, in PED-MERMAIDS, a paediatric trial on bacterial infections, and in NeoVanc, a study on neonatal sepsis.

The EPIICAL project achieved an important milestone by completing the enrolment target in the CARMA observational study, which aims to identify the factors that influence the responses to early treatment in children and adolescents.

Furthermore, our portfolio of projects is set to expand substantially in the year ahead with six EU funded project applications having been approved. Penta will lead two of these as the project coordinator, while being involved as partner in the other four projects.

With the aim of improving our governance, efficiency, quality and ultimately our impact, we have set in motion an internal reorganization process. We have reinforced our legal and administrative management capacity commensurate with our organizational growth. At the same time, we have created a dedicated area for data management. Moreover, we now have a communication strategy to enhance Penta's credibility and influence at international level.

As an organization, **we firmly believe in investing in our staff and giving young people an opportunity**. We have developed training options that allow for relatively quick yet enduring 'upskilling'. We have been applying this in our research too – and have pioneered young collaborators being part of study teams.

With this report we hope to share with you how we have been able to accomplish all this. Looking to the future, together we endeavour to identify new partnerships that will allow us to continue improving treatment and care of children. In this way, we can deliver on our **shared vision of a world where all children with infection get the treatment they need**.

We would like to acknowledge the dedicated work of our network of collaborators, the trust of our strategic partners, the commitment from our staff and the financial and operational resources made available by those who believe in our mission.

Our true strength lies within the Penta family – the invaluable commitment and enthusiasm of the youngest investigators and the Foundation staff.

Finally, a **special thanks to all the children and families** who have contributed to our activities and studies. We are working for them, but without them nothing is possible!

Carlo Giaquinto



1. ABOUT US





We are a **global
independent
scientific network**
dedicated to
paediatric
research

Our vision

**A world where all children
with infection get the
treatment they need**




Our mission

**To be a leading global
research partnership
working to transform the
prevention and treatment
of infection in children**



What makes us unique


One network
One vision
One voice



Our network of collaborators and investigators share our vision. We are all convinced of the power of our partnership and are serious about changing prevention and treatment options for children with infection everywhere – for good.

Our values


Sharing,
understanding
and belonging



We encourage and support the sharing and exchange of ideas, innovations, data and proposals within the network, and we value every contribution.

Our guiding principles

Inclusion, team
spirit, responsibility,
transparency



As an international collaborative platform coordinating and undertaking research designed to improve child health and combat infections – we include and respect investigators throughout our network. Making space for all those passionate about our mission is something we pride ourselves on - we seek to create a genuine platform for teams to build a body of research that counts for children's wellbeing.

Penta's history

Penta is an alliance of people united by a common vision



1. ABOUT US

The Paediatric European Network for Treatment of AIDS (PENTA) was **established in 1991** as a collaboration between paediatric HIV centres in Europe. The primary aim of the Network was to undertake independent clinical trials to address specific questions about antiretroviral therapies in HIV infected children.

Funding from the European Union, international organizations such as UNICEF and the World Health Organization, the pharmaceutical industry, the English Medical Research Council (MRC), France's INSERM and Italy's Istituto Superiore di Sanità (the research branch of the Ministry of Health) helped Penta investigators answer critical issues in HIV care.

Over time, as the network started to grow beyond just HIV, clinical trials and observational studies **Penta became an ideal platform to generate, develop and support research and training activities** – thus the Penta Foundation was born.

Recognising that other infections in children were similarly neglected, in 2011 Penta evolved into Penta ID (Infectious

Diseases), extending its research (both clinical and basic) to other paediatric infectious diseases. With the growing threat of antimicrobial resistance – Penta has since built an ambitious and unique agenda to tackle antimicrobial resistance, developing prevention and treatment strategies for children and newborns.

1991**Penta ID Network**

The Paediatric European Network for Treatment of AIDS

2004**Penta Foundation****2011**

Penta ID
Extension of network to address other IDs

2016

Penta ID Innovation
for profit spin-off

2019**Penta UK**



Our key partners

Penta's diverse range of activities is only made possible through our long-standing collaboration with 3 leading Clinical trials centres [MRC CTU at UCL](#) (UK), [INSERM](#) (France) and [PHPT](#) (Thailand)



1. ABOUT US

We have also entered into a number of framework collaboration agreements with other organizations that help us deliver our vision. In Italy key partners are **Padua Hospital (Azienda Ospedaliera di Padova)**, **Ospedale Pediatrico Bambino Gesù (OPBG)** in Rome and the not-for-profit research organization **Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF)**.

In Africa, we have a growing group of investigators and have recently signed a Memorandum of Understanding with our longstanding collaborator, **Joint Clinical Research Centre (JCRC)** in Uganda.

Moreover, we have also set up a partnership with the **Global Accelerator for Paediatric Formulations (GAP-f)**, an innovative collaborative model that will accelerate availability of optimized treatment options for infectious diseases, such as HIV, tuberculosis and viral hepatitis, affecting children in low- and middle-income countries.

We continued to be involved at regulatory level as member of the European network of Paediatric Research at the **European Medicines Agency (Enpr-EMA)**. At WHO Penta is part of the **Paediatric Antiretroviral Working Group (PAWG)** and **Paediatric Antiretroviral Drug Optimization (PADO)**.

Finally, we have teamed up with Virology Education, an established educational platform that will work with us in the implementation of future training programmes.

In 2018, we opened an office in Athens, Greece, in a space shared with the **Centre for Clinical Epidemiology and Outcomes Research (CLEO)**. Penta and CLEO have signed a Memorandum of Understanding and have begun collaborating on RANIN-KIDS (Reducing Antimicrobial use and Nosocomial Infections in KIDS: A European Network), which CLEO is coordinating and for which Penta is providing scientific and management support.

This is expected to be the first of many future collaborations between us.

We have **continued to develop new collaborations with industry**, both innovator and generic, on specific research and educational programmes.

[Padua Hospital](#)

[Ospedale Pediatrico Bambino Gesù](#)

[Consorzio per Valutazioni Biologiche e Farmacologiche](#)

[Joint Clinical Research Centre](#)

[Global Accelerator for Paediatric Formulations](#)

[European Medicines Agency](#)

[Centre for Clinical Epidemiology and Outcomes Research](#)

2018 at a glance



PROJECT APPLICATION
SUCCESS RATE

100%

PROJECTS
APPROVED 6 OUT OF 6



VALUE OF NEW PROPOSALS
SECURED IN 2019

38 M euro



TOTAL FUNDS MANAGED BY THE
FOUNDATION

185 M euro



TR@INFORPEDHIV
COURSES

7 WITH OVER
500 HEALTHCARE WORKERS
IN 7 COUNTRIES



EU FUNDED PROJECT
COMPLETED: EMIF

1

EUROPEAN MEDICAL
INFORMATION FRAMEWORK (EMIF)

*One platform for data discovery,
assessment and (re-use)*

Launched in January 2013, EMIF was a five-year project funded by the Innovative Medicines Initiative Joint Undertaking (IMI-JU) programme, tasked with improving access to, and use of, health data for answering important clinical and public health questions.

Its greatest legacy will certainly be data harmonization, with dementia and metabolic disorders also being key areas in this project.

The EMIF platform has allowed us to access data related to antibiotic prescription in children in 3 European countries in order to investigate the relationship between dose and weight in such prescriptions. The resulting data from this tool will provide for more accurate and appropriate prescriptions in the future.

Since we started



OVER

1000

CLINICIANS, RESEARCHERS,
SCIENTISTS



MORE THAN

110 31

ENROLLING SITES IN COUNTRIES



PEER-REVIEWED
SCIENTIFIC ARTICLES

100



35¹¹ 24

STUDIES

ONGOING
COMPLETED



MORE THAN

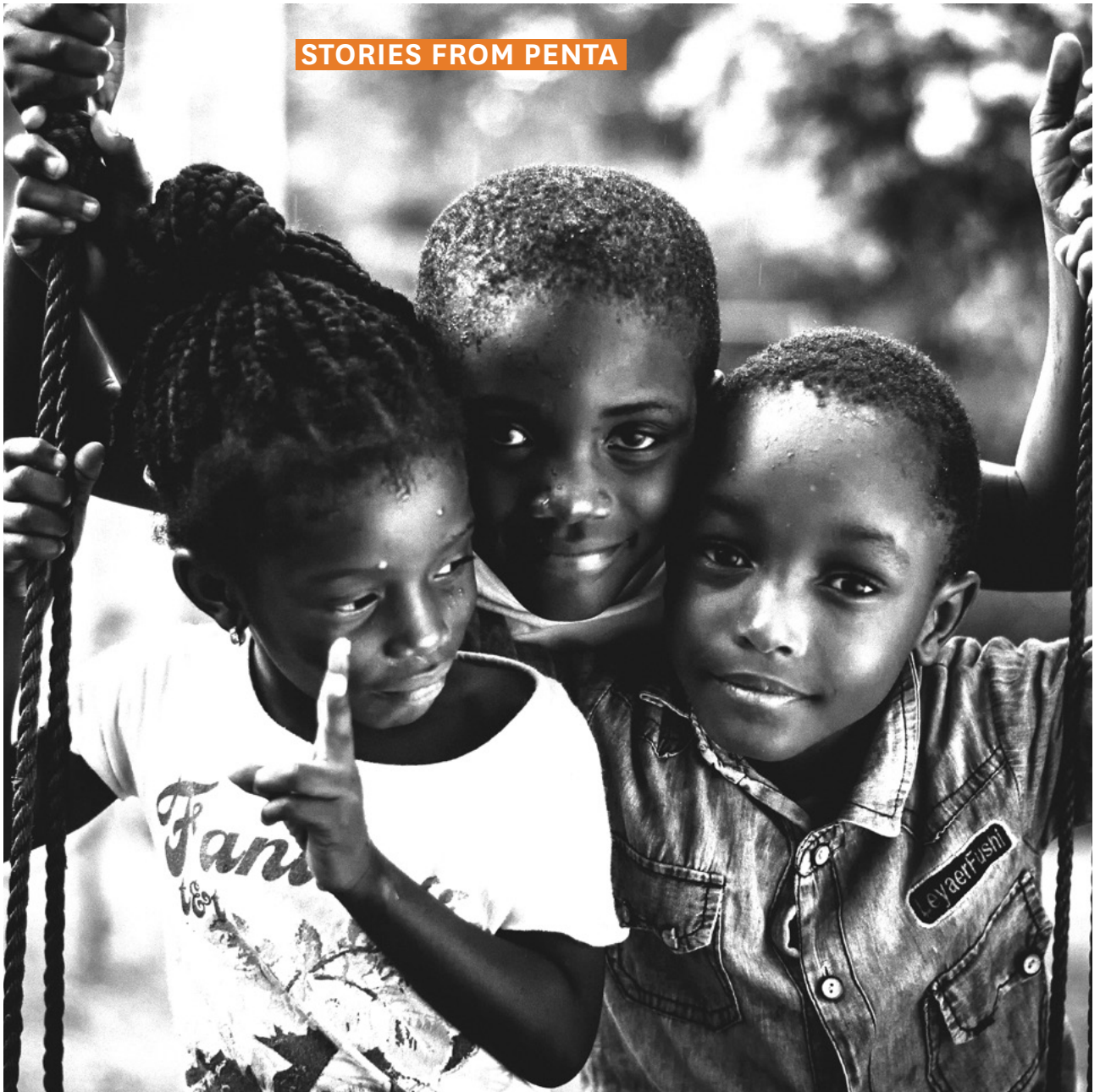
50000

WOMEN AND
CHILDREN ENROLLED
IN OUR STUDIES
(SINCE 2012)




PENTA FOUNDATION STAFF

34



**“AIDS is not a killer
because of
Antiretrovirals”**





Engaging young people in HIV research is crucial to understand and improve treatment outcomes

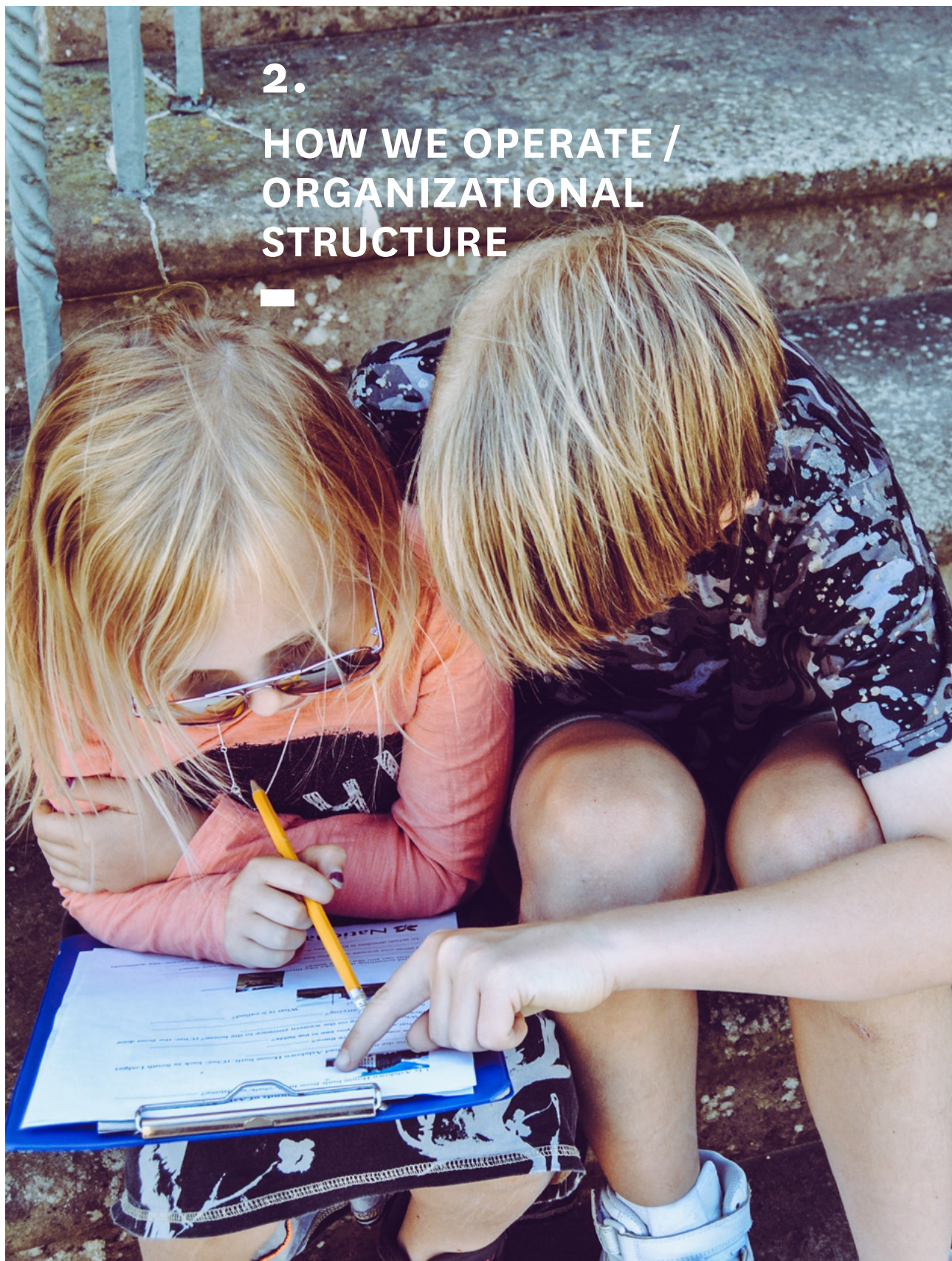
This story comes from CurARTE, a project led by Picturing Health (a UK non-profit organization making health related films) and Penta. It was undertaken with a group of young Malawian people living with HIV in order to find out why they had a hard time adhering to antiretroviral therapy and to offer them a safe space to explore their feelings. We believe that engaging young people in HIV research is crucial to really understand and improve treatment outcomes.

“There is a song still sung in Malawian primary schools, supposedly to create HIV awareness. Everyone knows and sing it. It says ‘AIDS is a killer, AIDS is a killer. AIDS is a killer. And that is why people die’. The young people worked on new words, modifying it to: ‘AIDS, AIDS, AIDS is not a killer. AIDS, AIDS, AIDS is not a killer, and that is why people live. And why? Tell me why? Because of antiretrovirals, because of antiretrovirals’. We sang it to the rhythm of rap.

(Tom Gibb, from the PicturingHealth project, during a workshop with HIV-positive adolescents in Malawi)

2.

HOW WE OPERATE / ORGANIZATIONAL STRUCTURE





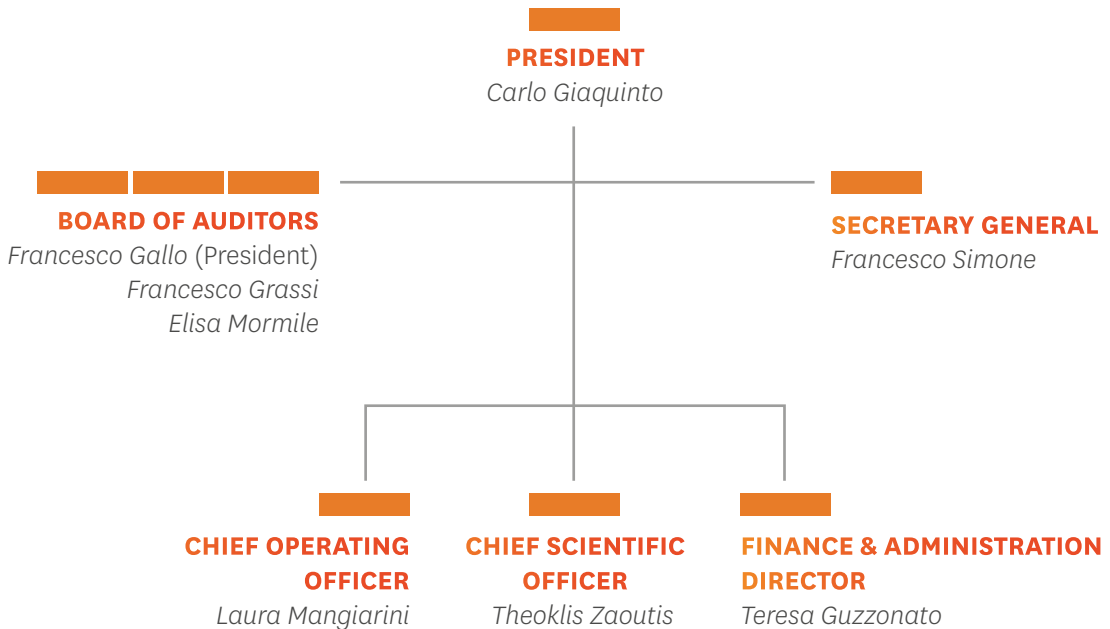
The flexible, multidimensional, Penta environment

Penta Foundation board

Members of the Board

The Foundation is managed by a Board of Directors consisting of no less than three and no more than eight members, who hold office for three years.

Carlo Giaquinto (*Chairman*)
 Diana Gibb (*Vice Chairman*)
 Mike Sharland (*Vice Chairman*)
 Paolo Rossi
 Claire Thorne
 Franco Zacchello



Penta Foundation staff

A wide range of personnel coming from 11 different countries based in 4 cities (Padova, Rome, London and Athens) is dedicated to the activities of the Penta Foundation. To meet the needs of our future projects and challenges, **Penta has been expanding**. New expertise was added in 2018, with an additional 11 positions - an increase of 47% over 2017 staff.

This is in large part down to the **extraordinary growth in activity** the Foundation experienced in 2018, leading to increased demands across the team. This is particularly true of the project management and financial planning & administration activities, as well as the Scientific expertise of the Foundation. As of 2018, we have 34 core staff members, while other external consultants have been added to cover project specific activities.



Penta Foundation operational areas

Grant office and Project management

The Penta Foundation provides overall administrative and legal support to new grant applications and to project implementation throughout the project life cycle, including application and coordination of large international consortia. From 2005 to 2018, we were involved in more than 35 major projects (approximately 50% EU funded and 50% from other donors) each of them including several partners from different regions and countries.

Data hosting, analytics and management

The Data team standardizes data management procedures for observational studies sponsored by Penta, ensure legal and regulatory compliance of all data management activities, including data archiving and secondary use of data, and build relationships to explore opportunities using 'big data'.

Training and Education

The Training team is committed to delivering high quality, comprehensive, tailored training courses globally. Penta understands the needs and complexities of doctors and researchers in the treatment and management of children, pregnant women and young people with HIV and have developed educational material to support their ongoing learning needs.

Communications Regulatory and Clinical

Our Communications Team coordinates the internal and external communications of the organization and across the network and beyond. Our communications are designed to ensure the work of the Penta Foundation and the Penta ID network translates scientific discovery and clinical research into messages that engage with and are best understood by their intended audiences. Future efforts will be directed towards the creation of further digital communication routes, implementing the existing platforms and thinking of new ones to reach an ever-increasing number of people who we can and must influence to achieve our vision of a world where all children with infection get the treatment they need.

The Regulatory & Clinical team interacts with the Project Team, providing guidance on ICH GCP guidelines and Ethical standards during project and protocol design and implementation. The team liaises with the Regulatory Agencies and Ethics Committees, and the European Medicines Agency for Paediatric Investigation Plan applications.

Penta ID Scientific Organization

2018 saw an exciting development as we started to reorganize the scientific work of the Foundation. Our scientific teams are now coordinated around thematic areas where Penta and our network feel we can add most value (HIV/TB, viral infections, fungal infections and antimicrobial resistance)

and also the key platforms where we operate (vertical transmission, basic science, education and pharmacology). We are doing this not only to ensure coherence and guide our scientific endeavours – but to develop the next generation of investigators.

Leading the scientific work of the Foundation, we have a scientific committee that includes key external experts, who meet to review and prioritize the scientific agenda and questions we will tackle. For each content area and platform there is a working group chaired by an experienced Penta researcher.

In 2019 we will develop our first consolidated scientific strategy which will hopefully bring to bear the full power and potential of the Penta network community.

CONTENT AREAS

PLATFORMS		HIV&TB	AMR	Fungal infections	Viral infections
	Pregnancy and vertical transmission	✓	✓	✓	✓
	Basic science & EPIICAL	✓			
	Data Management	✓		✓	✓
	Education	✓	✓		✓
	Pharmacology	✓			✓

3.

ACTIVITIES AND ACHIEVEMENTS





Not just clinical
trials, but cohort and
pregnancy studies
and educational
programmes


Objectives




Penta does so much more than clinical trials: we have extensive observational and cohort studies, pregnancy studies, a basic science platform across the different content areas, training and educational programmes, and a unique and ever growing network of investigators who are leading champions for child health in their home countries.

There is a growing sense that we should up our ambition and consider tackling other serious children's infections and we will be working on this in 2019.


In 2018 the objectives were:



Support clinical research to address HIV, antimicrobial resistance and other infections in women and children



Develop a coordinated platform of clinical and basic science investigators for child health and infections



Build the capacity of the network to undertake high quality research and deliver optimal clinical care

Research activities

Penta seeks to deliver **high quality meaningful research** – generating evidence that matters and makes a difference to practice. In our 27 years of operation we have developed considerable expertise in developing and running independent multicentre/multinational research projects that do just this

Our work on HIV has contributed to new treatment strategies and new drugs and drug combinations for children with HIV. This has made HIV in children a treatable condition – death is now the exception, while it used to be a certainty in the first year of life for most babies born with the virus. Our scientific studies may well take us closer to the elusive prospects of a cure.

Results from Penta studies have been used by companies for regulatory purposes – and **our efforts have decreased the time for drugs to be accessible by children in Europe, Africa**

and Asia. We are also building data systems that are critical to pharmacovigilance – which is the monitoring of the effects of medical drugs after they have been licensed for use. This is especially important to identify and evaluate previously unreported and unrecognized side effects.

In 2018 **we contributed vital data on what form of dolutegravir babies and children can take.** This helped WHO update its guidance for countries. Dolutegravir is an important HIV drug that is more effective, easier to take and has fewer side effects

than alternative drugs that are currently used. It also has a high genetic barrier to developing drug resistance, which is highly desirable for and necessary for children who face lifelong treatment. Further data expected in 2019 will ensure we know safe and effective doses for smaller children (under 20kg).

Penta also developed the [WHO toolkit](#) – designed to identify the challenges and solutions for promoting and accelerating timely and high quality research and development of antiretroviral drug formulations suitable for infants, children, adolescents and pregnant and breastfeeding women.

Our unique collaborative platform has expanded in recent years to include **observational and cohort study collaborations** and pregnancy studies that can address the vertical transmission of infections. When Zika was recognized as an emerging threat, Penta was the network able to quickly **pull together global expertise** in transmission dynamics and design surveillance systems and a platform to answer critical questions about the nature of the infection and its impact on babies.

Penta seeks to bridge the gap between science and trials and is developing studies to look at immunological and virological responses to treatment, microbiological studies including drug resistance and cohort-based studies to compare treatment and outcomes across different European countries. Recently, a basic science

platform has been established to create and manage a network of cutting-edge laboratories dedicated to the development and implementation of the following areas: molecular and cellular immunology, molecular microbiology, multi-omics technologies, microbiome and bioinformatics. With this platform, we intend to pursue discovery research on disease pathogenesis that will pave the way for the development of more targeted clinical treatments and drive ‘precision medicine’.

Currently, the Penta Foundation and its network are involved in research projects in various developing countries that address several critical neglected areas in infections in children **beyond HIV** and including arboviruses and antimicrobials.

We have been involved, as coordinator or partner, in a growing number of non HIV-related projects. In some of them, Penta, with its very well-established network of paediatric hospitals, represents a gateway for paediatric expertise. This is especially true in projects (such as EMIF, PREPARE or RESCEU) where the main research focus is on adults. This expertise is enhanced through our participation in large national networks as INCIPiT, the Italian Network for Paediatric Clinical Trials, whose mission is to foster and support the planning, conduct and completion of all types of clinical studies conducted in Italy in the paediatric population by profit or not for profit sponsors, and PEDIANET, an Italian primary care epidemiological network.



A day in the lab with Nicola Cotugno, a young investigator working in the EPIICAL project





“This complexity has greatly helped my personal growth”

“I became interested in HIV-related immunology after receiving my degree in Medicine and when, as a medical student, I began following vertically HIV infected children at the Bambino Gesù Children’s Hospital in Rome. During my residency in Pediatrics, back in 2013, I observed the first baby steps made by EPIICAL. I immediately sensed that EPIICAL was a great opportunity to pursue my passion for immunology research in order to contribute to future possible strategies aimed at improving the quality of life of HIV infected children.

Today, in the 3rd of the project, I am now actively involved in the research and clinical activities of the Immunological Platform for the EPIICAL studies (CARMA, EARTH and HVERRICANE) through scientific discussions, procedure validation and data dissemination.

I feel that this project, more than any other in which I have participated, has given young researchers like me the opportunity to share work experiences with great scientists and top-level physicians in the field of pediatric HIV from all over the world. On the other hand, however, EPIICAL is a broad and extremely diverse consortium which aims to merge knowledge from different fields. I now feel that this complexity has greatly helped my personal growth and adaptability in future collaborative projects. To young researchers I will offer this advice: Follow your passion, don’t let setbacks discourage your research, be determined... and try to do something EPIICAL!”

Ongoing projects

Penta now has a strong portfolio of ongoing research projects and a growing network of investigators



Projects in 2018

HIV projects and studies coordinated/ sponsored by Penta

EPIICAL

*Early treated
Perinatally HIV Infected
individuals: Improving
Children's Actual Life*

Purpose

To implement a predictive platform for the early identification of novel therapeutic strategies for HIV infected children

from 2016 until 2020

Penta budget
€ 8,561,664

Funder
ViiV Healthcare

PENTA 17 SMILE

*Strategy for Maintenance
of HIV suppression with
integrase inhibitor +
darunavir/ritonavir
in children*

Purpose

To evaluate safety and antiviral effect of a once daily integrase inhibitor administered with darunavir/ritonavir compared to standard of care among HIV-1 infected, virologically suppressed paediatric participants

from 2013 until 2020

Penta budget
€ 2,664,961

Funder
JANSSEN, GILEAD,
ViiV Healthcare

PENTA 20 ODYSSEY

*A randomised trial of
dolutegravir (DTG)-based
antiretroviral therapy vs.
standard of care (SOC)
in children with HIV
infection starting first-line
or switching to
second-line ART*

Purpose

To assess the efficacy and toxicity of dolutegravir plus 2 NRTI versus standard of care among HIV positive children and adolescents

from 2014 until 2021

Penta budget
£ 10,534,600

Funder
ViiV Healthcare

ETRAVIRINE

Purpose

The aim of this study is to collect long-term safety data on etravirine use in children and adolescents with HIV infection in a "real world" setting in Europe

from 2013 until 2018

Penta budget
€ 2,500,320

Funder
JANSSEN R&D

DOLOMITE

Purpose

To provide a comprehensive programme of work encompassing pharmacokinetics, usage and safety of dolutegravir in pregnancy

from 2018 until 2022

Penta budget
€ 3,998,340

Funder
ViiV Healthcare

Antimicrobial resistance projects

NeoVanc

Treatment of late onset bacterial sepsis caused by vancomycin susceptible bacteria in neonates and infants aged under three months

Purpose

To develop an optimal dosing and monitoring regimen for vancomycin use in preterm neonates and infants under 3 months of age

from **2014 until 2020**

Penta budget
€ 653,378

Funder
European Commission – The Seventh Framework Programme - FP7

COMBACTE-MAGNET

Combatting Bacterial Resistance in Europe - Molecules Against Gram Negative Infections

Purpose

To determine more effective treatment strategies for intensive care unit (ICU) infections, particularly with Gram-negative bacteria

from **2015 until 2021**

Penta budget
€ 1,725,013

Funder
European Commission – Innovative Medicines Initiative - IMI

NeoOBS

NeoAMR Observational Study

Purpose

To collect high-quality observational data to inform trial design and comparator selection for a clinical trial(s) to assess the efficacy of novel antibiotic regimens in areas with high endemic rates of antimicrobial resistance

from **2017 until 2020**

Penta budget
€ 2,621,420

Funder
GARDP

Other Viruses projects

ZIKAction

Preparedness, research and action network on maternal-paediatric axis of ZIKV infection in Latin America and the Caribbean

Purpose

To address key knowledge gaps relating to Zika virus epidemiology, natural history and pathogenesis, with a particular emphasis on maternal and child health

from 2016 until 2021

Penta budget
€ 620,807

Funder
European Commission - Horizon 2020

PREPARE

Platform for European Preparedness Against (Re-)emerging Epidemics

Purpose

To harmonise large-scale clinical research studies on infectious diseases, preparing rapid responses to any severe infectious disease outbreak and providing real-time evidence for clinical management of patients

from 2014 until 2021

Penta budget
€ 575,800

Funder
European Commission – The Seventh Framework Programme - FP7

RESCEU

Respiratory Syncytial virus Consortium in Europe

Purpose

To gather information on the scale of Respiratory Syncytial Virus (RSV) infection in Europe and its economic impacts, using this information to design best practice guidelines for monitoring of RSV and to shape future vaccination programmes.

from 2017 until 2021

Penta budget
€ 175,000

Funder
European Commission – Innovative Medicines Initiative - IMI2

EMIF

European Medical Information Framework

Purpose

To develop a framework for evaluating, enhancing and providing access to human health data across Europe

from 2013 until 2018

Penta budget
€ 194,656

Funder
European Commission – Innovative Medicines Initiative - IMI

Clinical research network and infrastructure building

ID-EPTRI

Infectious Diseases – European Paediatric Translational Research Infrastructure

Purpose

To propose developmental models for paediatric medicines that integrate technology driven aspects with clinical trials

from 2018 until 2019

Penta budget

€ 175,625

Funder

European Commission – Horizon 2020
ViiV Healthcare

C4C

Collaborative Network for European Clinical Trials For Children

Purpose

To develop a large, collaborative paediatric network that will facilitate the development of new drugs and other therapies for the entire paediatric population in Europe

from 2018 until 2024

Penta budget

€ 7,011,250

Funder

European Commission – Innovative Medicines Initiative - IMI2

By building paediatric clinical research networks and infrastructures, we can make progress towards our primary objective - to **facilitate the generation of information** needed to ensure that the right drug at the right dose is available for use by children and newborns. Through EU funding, Penta is contributing towards the development of a European network of collaborators which can facilitate the conduct of research concerning child diseases and drug development, together with the pharmaceutical industry.

In 2018, Penta started connect4children (c4c), an exciting 6-year project funded by the Innovative Medicines

Initiative 2 Joint Undertaking (IMI2 JU), Europe's biggest Public Private Partnership funded jointly by the European Union's Horizon 2020 research and innovation programme and the European pharmaceutical industry (represented by EFPIA, the European Federation of Pharmaceutical Industries and Associations). The project aims to promote innovation in the design of paediatric clinical trials and quantitative methods in order to foster the development of new medicines in rare paediatric diseases and high medical needs areas. The collaboration will address the fragmentation of efforts between sponsors, sites and countries, the paucity of

paediatric patients available for study and the need for multiple capable sites and expertise to make trials successful. Through the set-up of a sustainable, integrated platform c4c wants to facilitate an efficient and swift delivery of high quality clinical trials in children and young people across all conditions and phases of the drug development processes.

The **voices of children, young people and families** are a pivotal part of the innovative approach of c4c: we will place patients at the centre and assign them an active role in the development of the different clinical trials that we are going to conduct through the project.

New projects secured for 2019

PediCAP

Impact of duration of antibiotic therapy and of oral step-down to amoxicillin or co-amoxiclav on effectiveness, safety and selection of antimicrobial resistance in severe and very severe childhood community-acquired pneumonia (CAP): a randomised controlled trial (PediCAP Trial)

Purpose

To optimise antibiotic treatment for children aged 3 months to 10 years hospitalized with severe/very severe community-acquired pneumonia in South Africa, Uganda, Zambia and Zimbabwe

from 2019 until 2024

Penta budget
€ 792,756

Funder
European Commission - EDCTP2

BREATHER Plus

A randomised open-label 3-arm, 96-week trial evaluating the efficacy, safety and acceptability of weekends off dolutegravir-based antiretroviral therapy (ART) and monthly long-acting injectable ART compared to daily dolutegravir-based ART in virologically suppressed HIV-infected children and adolescents in sub-Saharan Africa

Purpose

To evaluate alternative strategies to treat HIV-infected adolescents in sub-Saharan Africa successfully without the requirement for daily oral therapy

from 2019 until 2024

Penta budget
€ 88,187

Funder
European Commission - EDCTP2

EMPIRICAL

Empirical treatment against cytomegalovirus and tuberculosis in severe pneumonia in HIV-infected infants: a randomized controlled clinical trial

Purpose

To develop an empirical treatment against cytomegalovirus and tuberculosis in severe pneumonia in HIV-infected infants

from 2019 until 2024

Penta budget
€ 571,420

Funder
European Commission - EDCTP2

ECRAID

European Clinical Research Alliance on Infectious Diseases

Purpose

To establish a coordinated and permanent European infrastructure for clinical research on infectious diseases

from 2019 until 2020

Penta budget
€ 165,150

Funder
European Commission - Horizon 2020

Value-Dx

The value of diagnostics to combat antimicrobial resistance by optimising antibiotic use

Purpose

To focus on the value of diagnostics to combat antimicrobial resistance by optimising antibiotic use

from 2019 until 2023

Penta budget
€ 298,250

Funder
European Commission - Innovative Medicines Initiative - IMI2

REACH

Research on HIV, tuberculosis (TB) and/or hepatitis C (HCV) in patients with mono-, co-infections and/or comorbidities in the context of fostering collaboration with the Russian Federation

Purpose

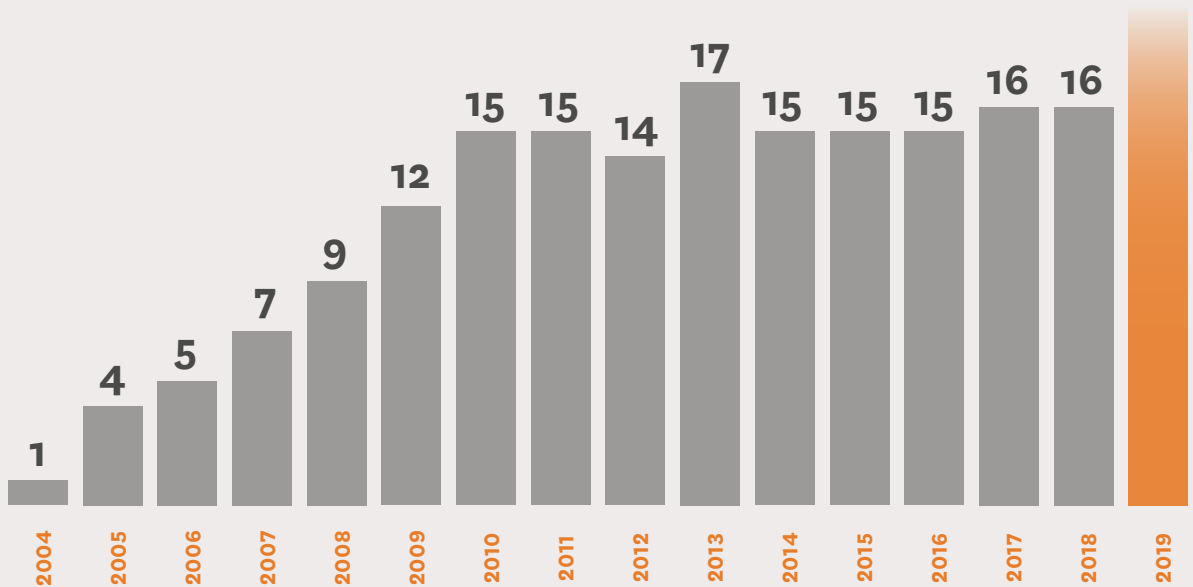
To address key research questions in the global health response to the epidemics of HIV, HCV and TB in the priority populations of pregnant women, children and adolescents

from 2019 until 2020

Penta budget
€ 1,056,734

Funder
European Commission - Horizon 2020

Numbers of projects (2004 - 2019)





“I learned not to blame myself”:
a story by the mother of a child
enrolled into the EARTH study,
which aims to document and
understand the natural history
of children with HIV who are
treated early



“With his participation in the study, I will help other children as well as my son”

“My name is Lina and I’m 31 years old. I am Domilique’s mother, who is 9 months old.

He was born with the virus. He got sick very soon and was admitted to the Matola Provincial Hospital.

Dr. Elsa – the pediatrician of the Paediatric Centre of Excellence told me about the EARTH study. I agreed for Domilique to participate in the study, most of all, because I wanted Domilique to take the Antiretrovirals and have a healthy life.

Today Domilique is well, growing up and healthy. He has put on so much weight that today it is hard to ‘nenecar’ – ‘carry him on my back’. Domilique has been going to the paediatric centre and participating in the study for 6 months. I understand that, with his participation in the study, I will help other children as well as my son. In the paediatric centre they are taking good care of Domilique and myself.

Although it is a bit far from my place, it is my wish to continue my follow up here because I feel that if I change then Domilique won’t have the same treatment and I’m afraid he could die. We feel special here at the hospital and we are lucky to have all the team supporting us. Fortunately, my family helps us as well. Everyone in my family, and also my neighbors, know that myself and Domilique are living with HIV; my mother is living with HIV too. When there is support within the family one can continue her own life and it becomes a normal situation. When I was pregnant I took the medication but my son got the virus. I learned not to blame myself for this and I promised myself I would always take care of Domilique. When he is able to understand, I will explain to him he has to take the pills in order to grow strong and healthy, just as my mother did to me, and have his dreams fulfilled.”



Other activities



Patient involvement

Increasingly it is recognized that patients, **including children and adolescents must be involved in research** – not just as passive beneficiaries. Penta has been pioneering in developing examples of how researchers can engage children and their families into the research work. These include:

- Sexual and relationship education programmes are aimed at increasing the skills of those working with HIV positive adolescents to be able to have conversations and give clear, factual information on sex and relationships. The delivery of these programmes help improve the wellbeing of adolescents living with HIV, providing them with all the information they need in order to empower them to make informed decisions about their sexuality and relationships freely and responsibly.

- Youth Trial Board is a pilot project nested within the Odyssey study to explore ways to meaningfully involve young people living with HIV in the development and delivery of clinical trials. Penta supports an interactive, youth-friendly programme with young people involved in the study across four different countries.

- Patient and Public Involvement is a cross-cutting scheme within the c4c project that gives an active role to patients' families and members of patient associations in the design and development of the different clinical trials that c4c will promote and conduct.

International cooperation projects

Since the early 2000s, Penta has been involved in the management of several international cooperation projects in low- and middle-income countries, in partnership with different Italian and international NGOs (such as Casa Accoglienza alla Vita Padre Angelo, the Romanian Angel Appeal Foundation and various hospitals and associations operating in the health and psycho-social care field in Eastern Europe and Sub-Saharan Africa) aiming to provide care to women, children and families in Africa and resource limited settings.

Quality Assurance

Penta takes quality seriously

– and we actively establish, manage and monitor systems for Quality Assurance in all our work.

Through our quality system, we ensure that the standards for all the study documentation are compliant with the Good Clinical Practice procedures and every type of collected personal data are compliant with the principles of newly approved European Data Protection Regulation. We also require that the same standards are adopted by our collaborators when working with us.

Education and training

Education is key to our mission. Penta remains committed to providing clinical training in paediatric HIV and other infections as part of its goal to improve clinical care for children, and to ensure robust high-quality clinical assessment as part of its trials. We also seek to ensure new investigators get trained and supported to run research, design their own studies and we plan to expand on this kind of capacity building in 2019 and beyond. The WHO toolkit for research and development of paediatric antiretroviral drugs and formulations, developed in collaboration with Penta, was a major step towards this.

The network has also developed [HIV Treatment guidelines](#) as a concise reference document for clinicians to guide antiretroviral choices for children and adolescents with perinatally acquired HIV.

Tr@inforPedHIV started in 2005, as a partnership between Penta and ESPID (European Society for Paediatric Infectious Diseases). It is a training programme for healthcare workers caring for HIV infected children, adolescents

and pregnant women. This pioneering course has integrated distance learning with interactive residential courses. Having delivered upwards of 50 training courses to date, and with a fully briefed faculty on board, Penta is able to deliver and tailor its innovative and high-quality training for a range of settings.

Since its initiation, more than 3,500 healthcare workers from over 30 countries have benefitted from our training courses. In 2018 alone we trained over 500 healthcare workers at residential courses in Durban (South Africa), St. Petersburg (Russian Federation), Antigua (Guatemala), Issyk-Kul (Kyrgyzstan), Rome (Italy), Zanzibar (Tanzania) and Odessa (Ukraine). See table 1 below for full list of courses.

Closely linked with our training activities is our collaboration with pTBnet (the European paediatric TB network). Penta helped organize and run the 2nd International Meeting on Paediatric TB in Vilnius, Lithuania from 21st – 23rd March 2018. Key members of the Penta Training team presented at the meeting.

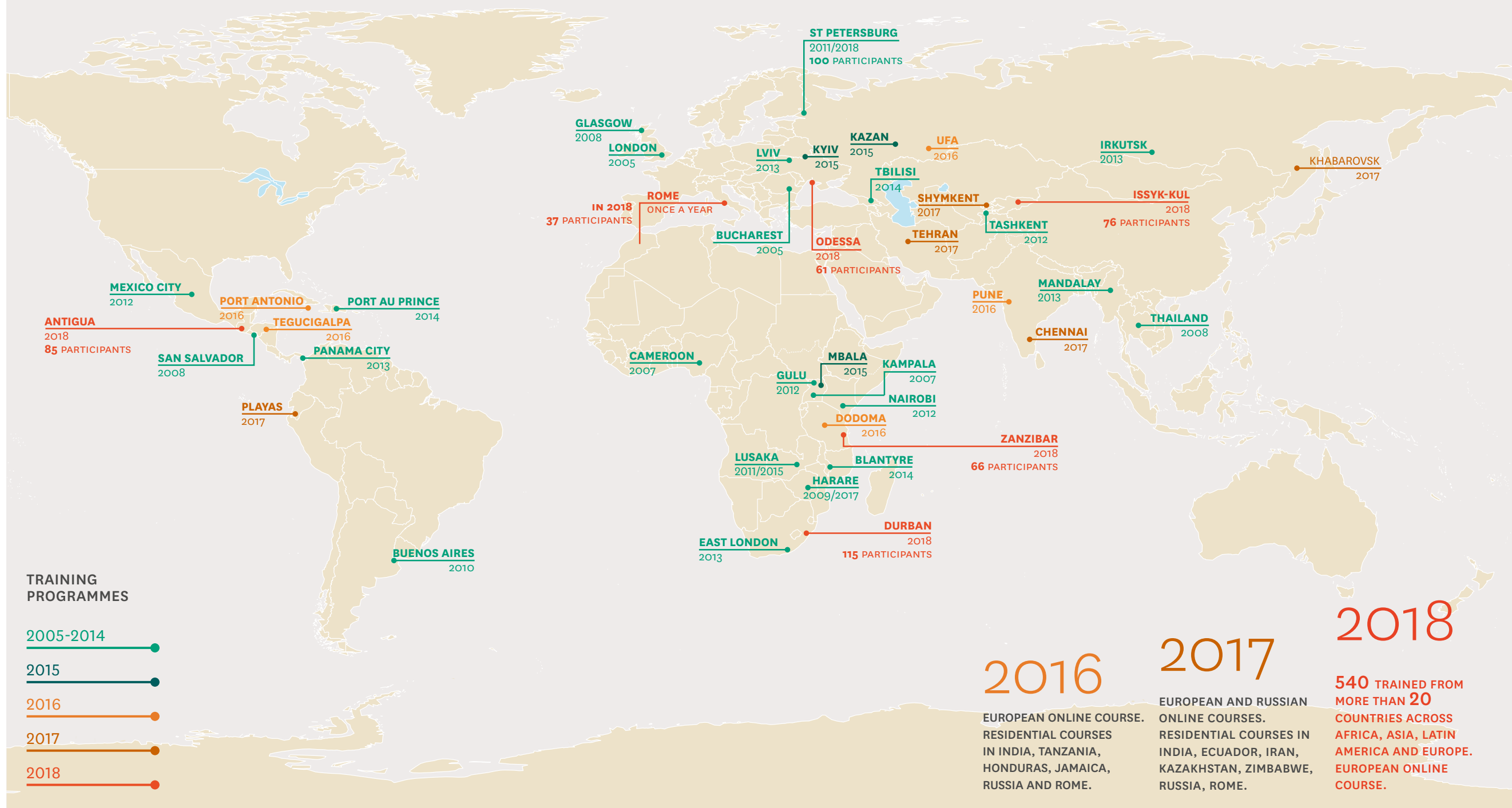
Penta has also developed a partnership with the well established Dutch educational organization, Virology Education. Together we have been working on identifying additional topics from non-HIV training programmes (such as Monoclonal Antibodies in Infectious Diseases, and Paediatric Transplant in Infectious Diseases).

“Penta not only trains, but exports collaborative research methods”

Some words from Penta trainer, Marisa Navarro (Hospital General Universitario Gregorio Marañón):

“Tr@inforPedHIV is much more than just a simple ‘educational activity’. Behind these courses lies the idea of the Penta network, the strong conviction that science and research are intended to improve quality of life of all people. Through Tr@inforPedHIV, Penta not only educates on advances in infectious diseases research but also exports collaborative research methods that can be easily be applied in everyday settings, thus helping clinicians and patients all over the world.”

Tr@inforPedHIV Training courses 2005-2018



4.

THE FUTURE: CHALLENGES AND OPPORTUNITIES





Following a
successful year,
our activities
in 2019 are focused
on **organizational
growth** and
continuing to
strengthen **network
capabilities**

4. THE FUTURE: CHALLENGES AND OPPORTUNITIES

Antibiotics are the most widely used drugs in young children – yet **less than 3% of antimicrobials are licensed for use in young children**. There is growing recognition worldwide that we have to get on top of the use of antibiotics and the emergence of antimicrobial resistance. Nowhere is this more of a threat than in newborns and young babies. The pipeline of antibiotics is non-existent and the barriers to finding new treatments for children look unsurmountable. The strong progress made in antivirals seems impossible and unachievable for antimicrobials. Penta will work to develop greater depth and strength in our work on in this area in 2019.

Our growing experience in vertical transmission needs to be explored further. Our work on Zika has shown we can adapt and provide useful tools and capacities quickly and efficiently and we will call upon our networks again.

In early 2020 funding for the HIV Clinical and Experimental platform EPIICAL will come to an end. The project, which aims to design and implement a predictive model for the early identification of novel therapeutic strategies for HIV infected children, has been supported by ViiV Healthcare, and, looking beyond EPIICAL, we hope to continue our fruitful collaboration. In 2019 we will finalize the results of the first four years and plan the activities for the 2020-2024 period to be presented to ViiV and the wider world.

Given the significant progress in other antiviral therapies (HIV, hepatitis C and hepatitis B) in adults and expanded birth dosing for hepatitis B – Penta will consider how we can contribute in other serious viral infections. We will also examine how and if Penta should take on some of the other neglected childhood infectious diseases.

We will also seek to strengthen the depth and quality of our work in clinical research. In doing so, we can **build evidence of what works for children** – and use this evidence to bridge the gap between adults and children's access to safe and effective prevention and treatment for infection.

We will work tirelessly towards growing, consolidating and expanding our network of investigators and trial sites. We will explore how to bring more countries into the network, especially low- and middle-income countries.

We are also planning to define and finalize the role of Penta as the research network within the Global Accelerator for Paediatric Formulations (GAP-f). Together, we are working to prioritize products, streamline the generation of clinical evidence, incentivize manufacturers, and accelerate product development.



Penta UK

In line with our growth, in 2019 the Penta Foundation is going to expand by setting-up a branch office in the UK.



Penta ID innovation

Penta ID Innovation was designed to create a bridge between industry and academia to facilitate the development of new therapeutics for children.

The spin-off company of the Penta Foundation, it offers a variety of services ranging from consultancy on specific studies to the full implementation of clinical studies sponsored by industry. It is designed to further the mission of Penta and overcome some of the hurdles that can come with new therapeutics for children.

2018 was a fruitful year for the company since the first consultancy services were successfully provided. The aim in the medium term is to develop a full-fledged Site Management organization (SMO) capability which is able to use the untapped potential of the Penta ID network. The objective for 2019 is to increase collaboration with pharmaceutical companies while focusing on the following actions:

Finalise the Quality Assurance system

Formalise the network of Penta sites to perform studies

Develop a marketing strategy

Start the collaboration with CROMSOURCE (a Contract Research Organization)

Write and submit the first Paediatric Investigation Plan (PIP)

Future collaborations

CUAMM

Doctors with Africa

Founded in 1950, it was the first non-governmental organization focused on healthcare to be recognized by the Italian government. It is now the country's leading organization working to protect and improve the wellbeing and health of vulnerable communities in Sub-Saharan Africa.

Penta and Doctors with Africa [CUAMM](http://doctorswithafrica.org) will collaborate on projects to protect and improve the wellbeing and health of vulnerable communities in Sub-Saharan Africa. This includes the training of local researchers and doctors, the development of policies, information systems and organizational models concerned with child healthcare, infectious diseases (HIV/TB/Malaria), nutrition and chronic non-transmissible diseases. In doing so, together we will strive to ensure the highest ethical standards, quality levels and protection of data in any area of research and activity that we jointly carry out.

doctorswithafrica.org

MUJHU

Makerere University John Hopkins University Research Collaboration

Established in 1922, Makerere University is one of the oldest and most prestigious English Universities in Africa. It currently acts as an enrolling site for clinical trials focused on HIV and paediatric pneumonia. The upcoming collaboration between Penta and MUJHU aims not only to ensure the delivery of the best care to sub-Saharan African children, but also to engage a younger generation of paediatricians and scientists who could become future leaders in paediatric trials.

mujhu.org

GARDP

Global Antibiotic Research & Development Partnership

GARDP is a not-for-profit R&D organization that addresses global public health needs by developing and delivering new or improved antibiotic treatments, while endeavouring to ensure their sustainable access. Initiated by the World Health Organization and the Drugs for Neglected Disease initiative (DNDi), GARDP is an important element of WHO's Global Action Plan on Antimicrobial Resistance that calls for new public-private partnerships to encourage R&D of new antimicrobial agents and diagnostics. GARDP's programmes on sexually-transmitted infections, neonatal sepsis, paediatric antibiotics and antimicrobial memory recovery, evaluation and exploratory research are designed to address global public health priorities.

Penta and GARDP are designing a common plan of action for 2019 to tackle serious and drug-resistant infections in children. The aim of the collaboration is to accelerate development of antibiotic treatments for children including: clinical trials designed to meet regulatory requirements, and trials with a focus on public health interventions to inform treatment.

gardp.org

As we set our sights to the years ahead, we are looking forward to:

Bringing greater rigour and science to our work. We will develop an organization wide scientific strategy – with agreed priority questions identified.

Establishing new partnerships. We are always eager to build new connections, and increase and encourage the exchange of data and proposal ideas.

Setting-up a branch office in the UK. This will help in further developing the network and existing collaborations, promote new research projects and project funding.

Strengthening collaboration with patient organizations.

We are committed to child health and we strongly believe that we have to listen to children and their families' needs, working both for and with them.

Expanding the scope of our activities. Health is a human right and we see the c4c platform as a potential game changer in Paediatric research.

5.



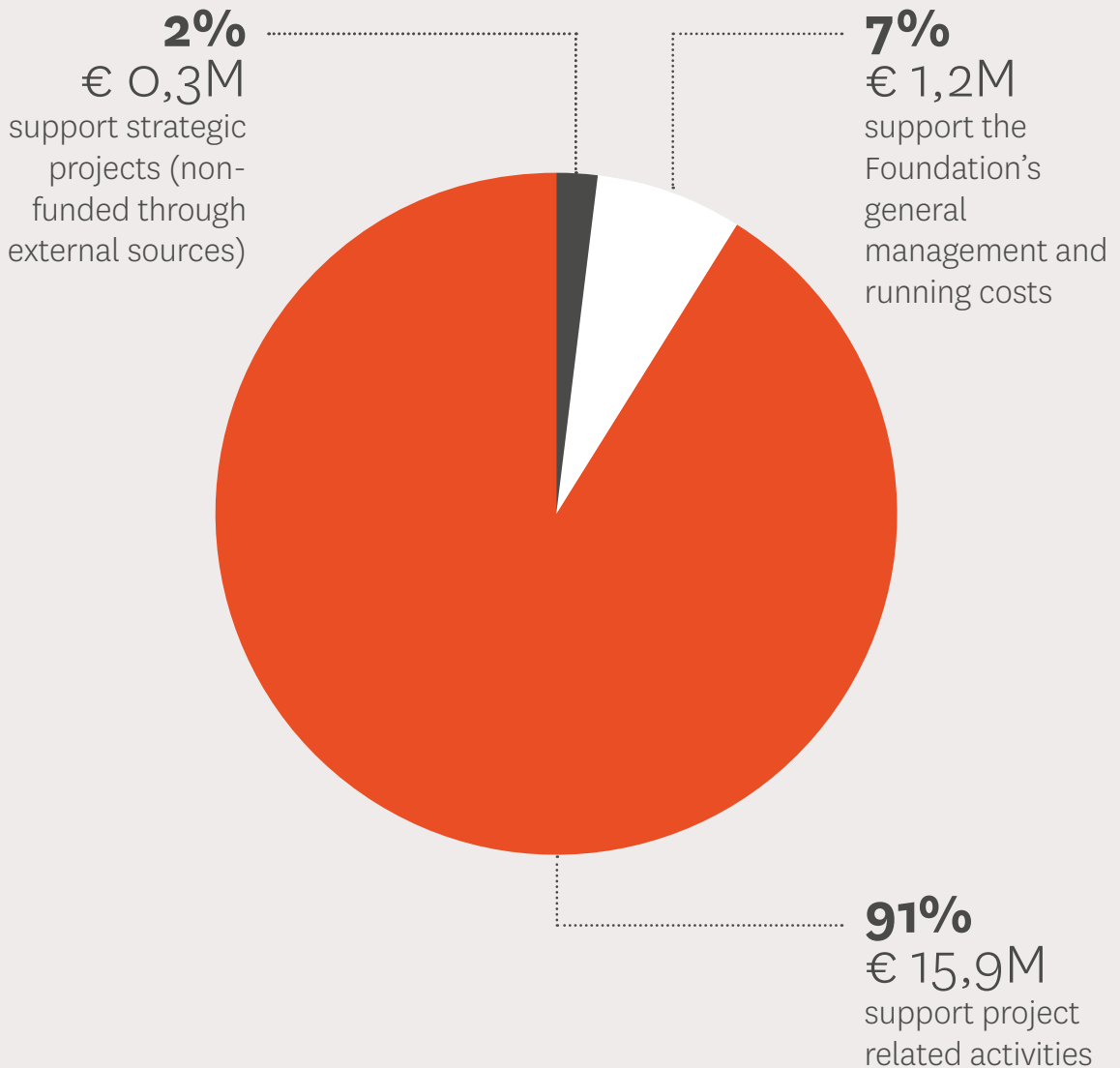
FINANCIAL RESULTS





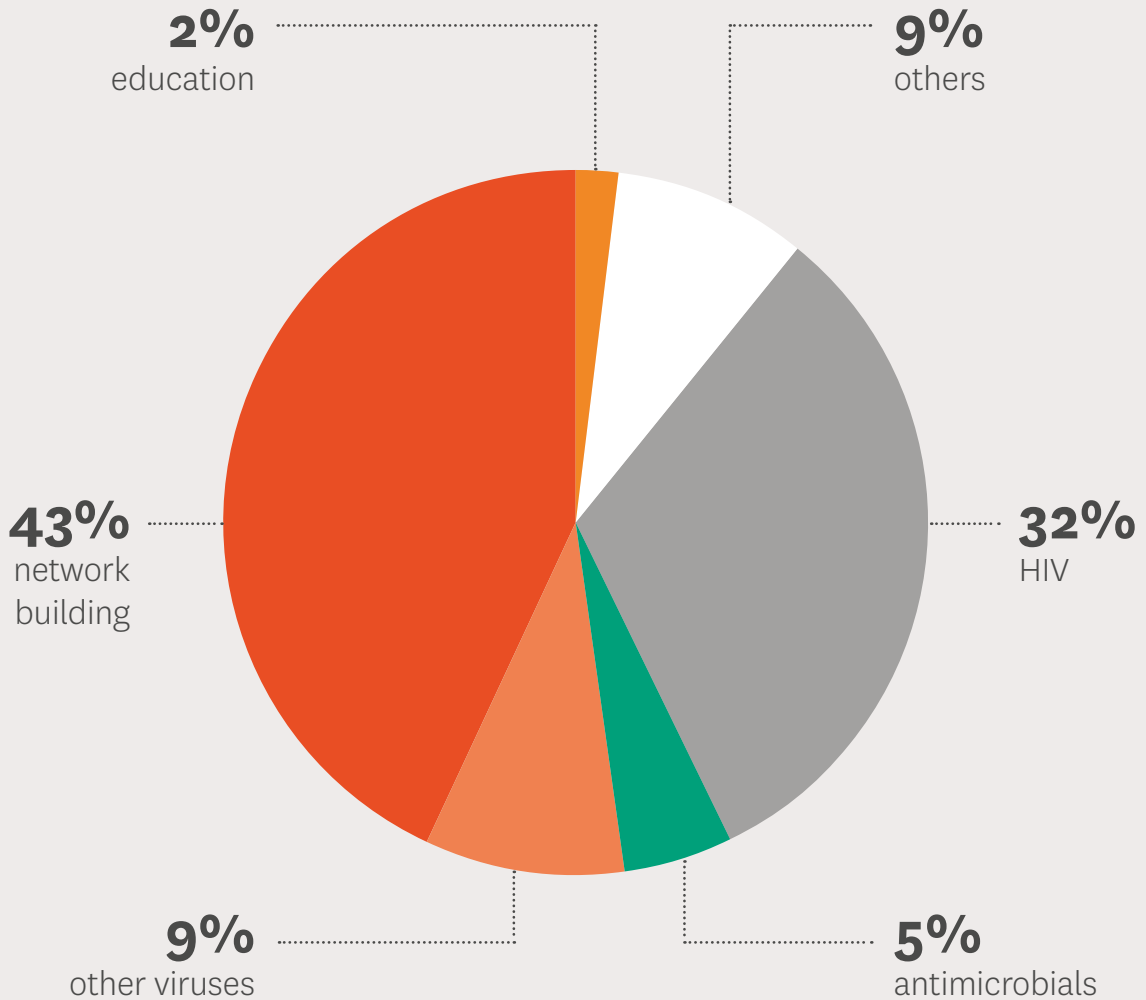
Our activities
are entirely
financed by **public
and private
contributions**
from international
organizations and
industry

Resource distribution



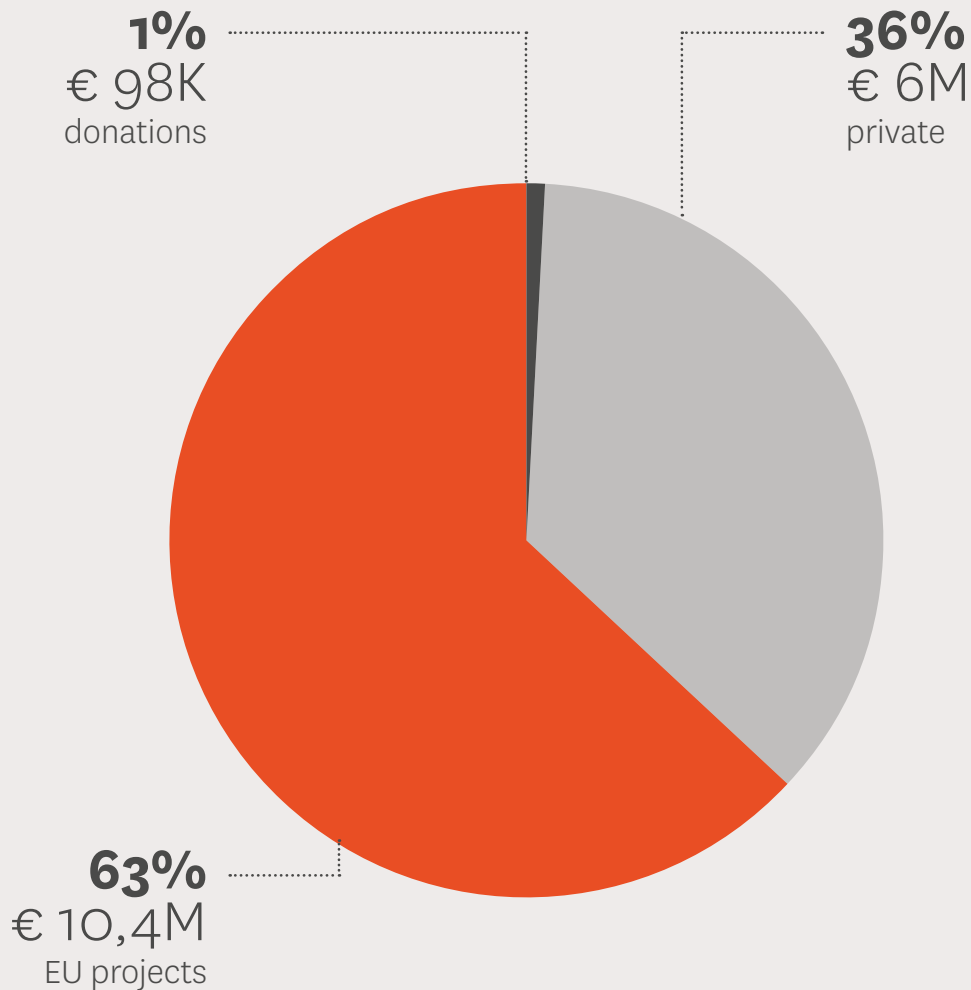
THE CHART SHOWS THE PERCENTAGE DISTRIBUTION OF THE RESOURCES BY THE FOUNDATION FOR 2018.

Expenses by research area



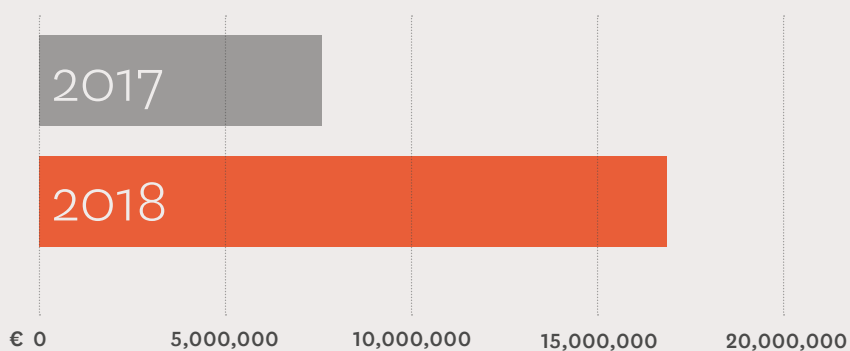
THE CHART SHOWS THE PERCENTAGE DISTRIBUTION OF THE EXPENSES INCURRED BY RESEARCH AREAS IN 2018. CLINICAL RESEARCH NETWORK AND INFRASTRUCTURE BUILDING IS NOW THE LARGEST AREA SUPPORTED - WHICH IS LARGELY EXPLAINED BY THE NEW conect4children PROJECT. HIV CONTINUES TO BE A KEY AREA OF RESEARCH.

Incomes by source



THE CHART SHOWS THE PERCENTAGE DISTRIBUTION OF THE INCOMES RECEIVED BY SOURCE OF FUNDING IN 2018. THE HIGHEST PROPORTION CORRESPONDS TO EUROPEAN-FUNDED PROJECTS WHICH IS ATTRIBUTABLE TO THE conect4children PROJECT. DONATIONS ARE NOT A SIGNIFICANT SOURCE OF FUNDING.

Revenues



REVENUES HAVE INCREASED BY 123% IN 2018 WHEN COMPARED TO 2017. THE MAIN REASON FOR THIS IS THE LAUNCH OF THE **conect4children** PROJECT OF WHICH PENTA IS THE GRANT COORDINATOR.

Financial audits

The organization financial statements are regularly audited and certified by the Board of Auditors, which is composed of 3 professionals appointed by the Board of Directors. For 2018 no irregularities have been identified by the Board of Auditors.



Index

<i>Letter from the President</i>	2		
1. ABOUT US	4	4. THE FUTURE: CHALLENGES AND OPPORTUNITIES	42
Penta's Model	6	Penta UK	45
Penta's History	8	Penta ID Innovation	46
Our key partners	10	Future collaborations	47
2018 at a glance	12		
Since we started	13	5. FINANCIAL RESULTS	49
2. HOW WE OPERATE / ORGANIZATIONAL STRUCTURE	16	Resource distribution	51
Penta Foundation Board	18	Expenses by research area	52
Penta Foundation staff	19	Incomes by source	53
Penta Foundation operational areas	20	Revenues	54
Penta ID Network		Financial audits	55
Scientific Organization	21		
3. ACTIVITIES AND ACHIEVEMENTS	22		
Objectives	24		
Research activities	25		
Ongoing projects	28		
Projects in 2018	29		
New projects secured for 2019	33		
Other activities	37		



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