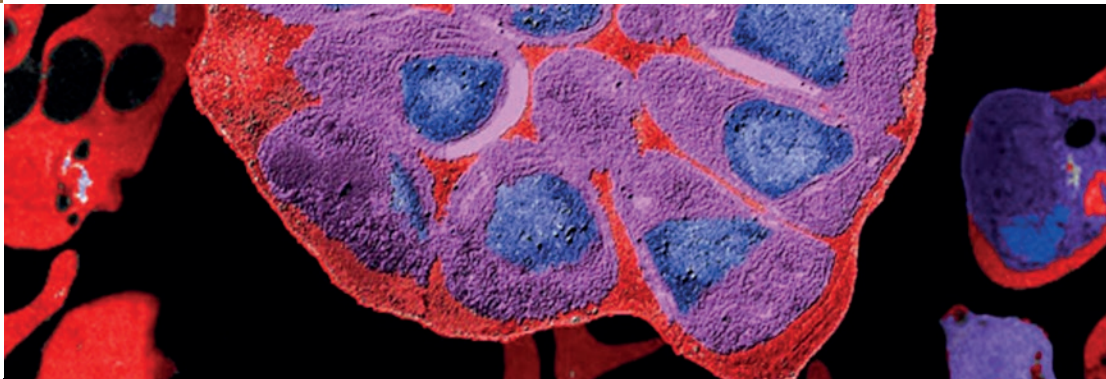
2020

Building a scientific strategy for the Institut Pasteur International Network

INSTITUT PASTEUR
INTERNATIONAL NETWORK



INSTITUT PASTEUR INTERNATIONAL NETWORK

Building a scientific strategy

Executive summary

The historical circumstances that have led to the development of the first international group of Pasteur Institutes after the Institut Pasteur (IP), are well known. These sui generis entities drove in their respective host countries major discoveries in microbiology, which they successfully put into practice to combat infectious diseases and epidemics. The trust by people in these institutes and their charitable mission enabled them to withstand the major upheavals of the first half of the 20th century and to overcome the turmoil of the charitable mission. Later on, the IP Network (referred to below as “the Network”) spread to new countries, especially in Asia and South America, always at the request of the National Authorities of the candidate country. These developments bear testimony to the continuing appeal of the research institutional model represented by IP, a model that combines scientific quest with public health action, translating new discoveries into intervention tools. The Network was further bonded by common values defined in the Institut Pasteur International Network charter and Collaboration Agreement, and by adhering to the principle of scientific solidarity between its members. A multifaceted partnership emerged, and led to powerful outcomes: transfer of knowledge, training of young scientists, conducting joint research programmes, exchanging researchers, providing financial and technical support where needed as well as assistance in emergency situations.

The Network is maturing and diversifying but more is to be done if one aims at better reflecting the global dimension it has acquired today. New perspectives should drive the Network far beyond the mere sum of the local actions carried out by the member institutes at their respective national levels. The Network should be mobilised around few federating research and public health programs to be recognised by the international community as a key research player in life sciences, capable of having an impact on major public health decisions.

At the Ravatys meeting, June 2016, the Board of IPIN Directors recommended building a scientific strategy that supports this ambition. A Steering Committee was established to elaborate a plan to strengthen our actions as a structured network and to highlight the actions that the Network, better than others, could implement and lead. The main recommendations were presented, discussed, and endorsed during the 49th meeting of the board of directors held in Institut Pasteur of Cote d’Ivoire, September 26, 2017.

The agreed strategy is justified in the present document. It is based on four major strands to guide the future developments of the Network :

- Implementing a «One Health» approach to explore endemic or emerging zoonoses.
- Investigating vector-borne diseases to improve methods of vector control.
- Studying the Mother-Child health issues and other health challenges in the young children.
- Exploring the impact of aging/longevity on health.

Importantly, by developing a problem-solving approach, the Network would generate results that could rapidly be translated into curative and preventive actions that improve the health of populations.

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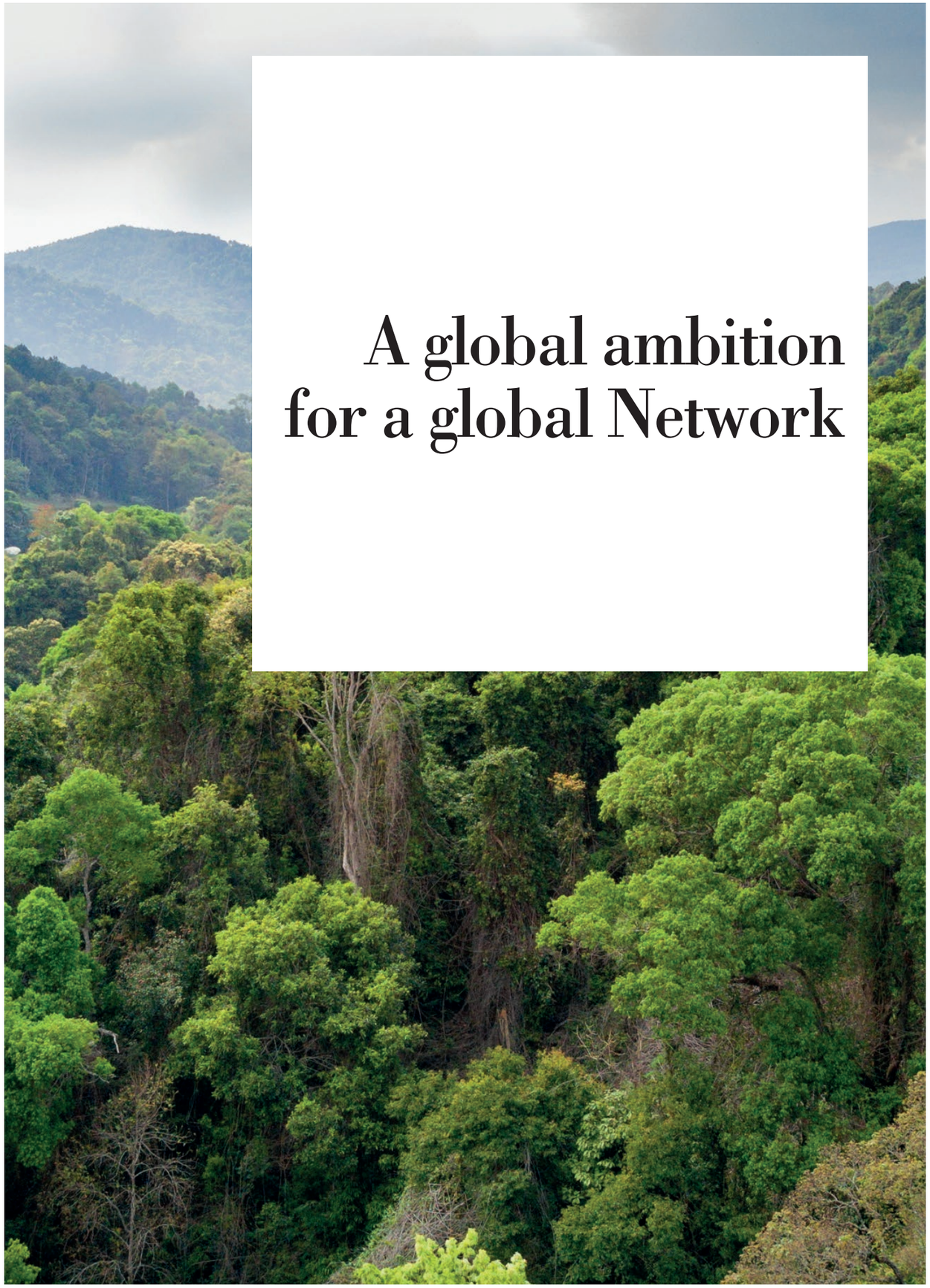
This document was written by Koussay Dellagi, on behalf of the Steering Committee for the Scientific Strategy of IPIN (SCSS).



A global ambition for a global Network

1
Which partnership modalities would consolidate IPIN as a global network?

2
The main asset to realise the Network's ambition: a facilitated access to the global diversity over large territories and ecosystems.

3
SWOT analysis related to the positioning of the Network.

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Which pertinent criteria should guide the selection of major joint actions?

1

Which partnership modalities would consolidate IPIN as a global network?

According to a logic of complementarity, the partnership was historically structured within the Network around the IP research groups in Paris. These groups thereby benefited from the privileged access to infectious diseases and pathogens in the Network countries, mainly former French colonies. These countries have access to, and benefit from, the advanced analytical and investigative capacities of IP. As a result, since the early days of the Network, collaborative programmes have been implemented within the Network which had essentially a public health dimension. They have generated original research that guided the implementation of pertinent health measures, and supported the training of the local scientific staff. Quite recently, some of these programmes took on a new dimension, shaping a multi-site regional partnership, a development illustrated by research programmes such as Karma (monitoring of antimalarial drug resistance markers), Birdy (neonatal infections and antibiotic resistance) and SEAe (encephalitis in Southeast Asia). Such diversity of research programmes, to which the Network offers access, has produced a real impact on public health. In addition, several capacity building projects were implemented within the Network: training courses, provision of internal grants, support for mobility, the creation of 4 years group young researcher programme, research grants such as ACIP (Inter-Pasteurian Concerted Actions) and PTR (Transversal Research Programs), career monitoring. Together with the efforts of the host countries in improving national education and health, they resulted in a more balanced commitment of all the Network partners in research activities and project management.

More recently, technologically advanced Institutes have emerged within the IPIN, engaged in research programmes with a more fundamental or biotechnological nature, that gave the Network a new dimension. This development was accompanied by a more systematic approach to exploit intellectual property equitably shared across the collaborative programs.

The emergence of such research projects within the Network, most often result from the researcher's initiative in response to a call issued by a national or international funding agency. By necessity they are focussed on specific research questions and cover only limited aspects of the targeted health problem. Unfortunetaly, the limited scope of this funding does not permit addressing the complexity of disease determinants adequately. In fact, these bottom-up approaches create real benefits when they are coordinated within an existing multi/transdisciplinary framework, factoring in new emerging concepts and rapidly changing knowledge and techniques. This concerted approach is best conducted at an institutional level, or by a group of institutions that can pool their expertise. Updated research agendas and health priorities are regularly published by international health or scientific authorities, but the Network has been almost absent from such high-level discussions.

In a time of globalised perspectives, the Network aspires to become a key player to develop new approaches and a global research agenda. By taking on some global health challenges, it should focus on its specific contributions to the international community. By better pooling scientific, technological, and material resources across its member institutions, the Network would be recognised as a proactive, coordinated and synergistic body. In order to achieve this, the Network institutions must agree on priority areas of action, and how to organise large consortia conducting ambitious research and intervention programmes. They must also be capable of coordinating large-scale and long-term data collection, establishing joint platforms for data sharing and biobanking, all key conditions to convince major public and private donors to fund their programmes.

THE INSTITUT PASTEUR INTERNATIONAL NETWORK

Comprising 32 members, the Institut Pasteur International Network is active on five continents. Leveraging its vast scientific and human community, the Institut Pasteur International Network takes part in national and international research, public health and education programs.

2

The main asset to achieve the Network's ambition: a facilitated access to the global diversity over large territories and ecosystems

The IPIN institutes are distributed across at least **four well-contrasted biogeographical systems:** Temperate humid ecosystems (European group), arid/desert ecosystems (Maghreb-Iran group), tropical, humid and warm ecosystems (Sub-Saharan Africa, South East Asia, the Amazon Basin groups) and island ecosystems (New Caledonia, Madagascar and the South-West Indian Ocean Islands, Caribbean Islands groups). Some of these regions are **biodiversity hotspots** where the bulk of the planet's endemic or indigenous wild fauna and the microbial flora associated to them, can be found. **Access to these ecosystems spread over five continents gives the Network's research teams an exceptional advantage to study the transmission of infectious agents across different ecosystems, including biotic and abiotic factors that modulate their distribution and dynamics globally.**

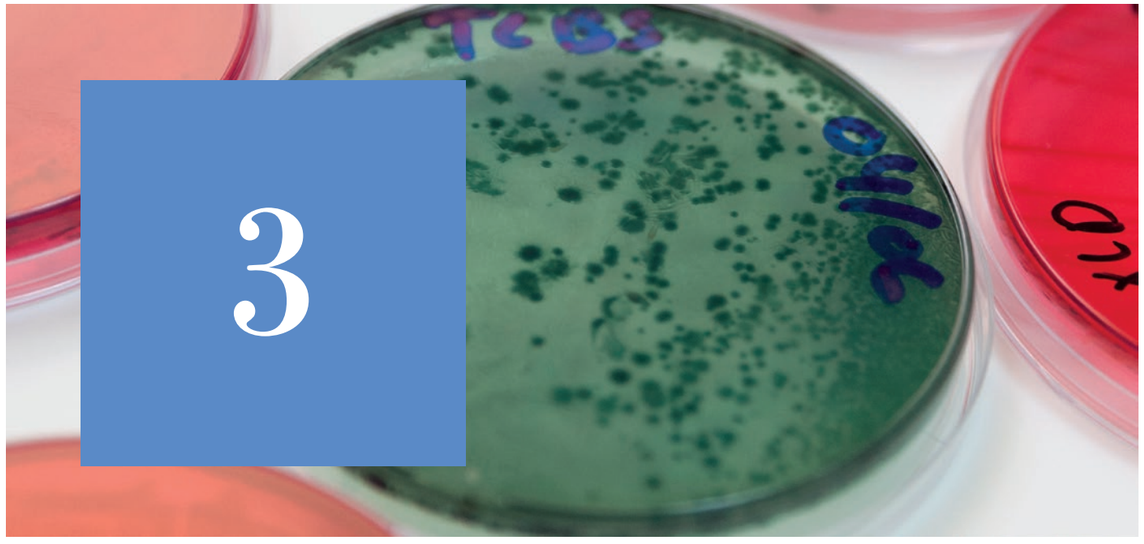
All conditions are in place to put the Network in a privileged position for the research on infection ecology at the international level. The Network should **coordinate collaborative studies across its members** on an unprecedented scale, taking advantage of available high throughput tools, the microbial, viral and parasitic diversity, to capture the changing nature of infection. A One-Health approach deployed in biodiversity hotspots will give access to endemic animal reservoirs (not only rodents and bats, but also other barely explored taxonomic orders) and arthropod vectors. This allows for an elucidation of the patterns in pathogen transmission between species and the co-evolution between these pathogens and their animal reservoirs. The Network will monitor the molecular dynamics of infectious agents as they spread globally. Large comparative studies in contrasted ecosystems will enable the member institutes to investigate how transmission cycles are influenced by changes in the natural environment caused by human activities (urbanisation, extensive or intensive farming, dam building, forest fragmentation), the introduction of invasive species (animal or vector) or the effects of climate change (distribution and biology of vectors). The Network can become a key partner in the global monitoring of antimicrobial resistance, drawing detailed maps of emergent hotspots, and exploring the mechanisms of resistance that emerge and spread in different ecosystems and under diverse conditions.

The Network programmes should explore the impact of genetic and epigenetic factors in exposed populations in the context of diverse comorbidities, co-infections, changes in the symbiotic flora (microbiome, virome and other parasitome). These co-factors may interfere with the natural history of transmissible or non-transmissible diseases, modify their clinical expression, modulate the host immune response against pathogens and the quality of response to vaccinations, and also influence the performance of diagnostic tests according to the singular past exposure of each investigated population.

Thanks to their national legitimacy, the Network institutions will efficiently recruit patients within their respective countries to participate in international studies and clinical trials, with the required support of local health authorities and ethical clearance. The Network could thereby mobilise powerful patient and population cohorts from diverse socio-economical, cultural, environmental and genetic backgrounds, offering greater significance to trials results

These major programmes conducted by Network institutions which have a long tradition of working together will produce more reliable data sets. Standardisation of applied methodologies, protocols and analytical tests calibrated against common references, will faciltate such collaborative resarch progammes.

The diversity of samples accessible to the Network institutions will be collected and preserved in a network in well-equipped and well-managed **local biobanks**, guided by common policies and supported by their respective national authorities. To facilitate the exchange of biological specimens, a **Pasteur International Biobank Network** will coordinate the local biobanks according to an appropriate governance model, according to international regulations. Reference **serum banks** will be created that are representative of the populations and ecosystems diversities, which will enable rapid evaluation of diagnostic tests in different settings. The added value of such serum and tissue biobanks backed by research centres with recognized diagnostic competences is immense, and represents one of the key assets that the Network could highlight to promote its strategy.



3

SWOT analysis related to the positioning of the Network

STRENGTHS

• The Network has a global dimension represented by 32 institutes located in 25 countries spread over 5 continents with several thousand researchers engineers and technicians.

• The Network member institutes have similar missions in public health, connecting diagnostic and research laboratory activities, with access to exposed populations across diverse environments. They have solid experience and expertise in translational research.

• Most institutes invest in applied and public health research but some institutes conduct basic research served by well-equipped technicalogical platforms.

• The Network institutions have a national legitimacy as well as the attention and goodwill of the national health authorities in their respective countries, making it easier to receive the approvals for collaborative programmes.

• The Global geographic coverage of the Network offers a unique wealth of observations and privileged access to local biodiversities and to various determinants of health problems, human and/or animal (individual, societal, environmental, climatic, etc).

WEAKNESSES

• **The Network is still perceived from the outside, as one that is more formal than functional/interactive;** a sum of institutes, primarily well-versed in their national missions, and interacting bilaterally with the IP in Paris rather than with the other institutes. However, efforts toward regional substructures are beginning to bear fruit by creating regional connectivity and dynamics.

• The Network is characterised by a **great heterogeneity, an aspect** that may hamper the organisation of major consortia. This heterogeneity concerns: i) the host country development level (80% are intermediate/low income countries), ii) the status of the institution (public/private), iii) their affliations/accreditation towards respective ministries/ departments (Education and Reseach/Health or both), iv) the official missions they are in charge of (biological operator with or without any role in epidemiologic monitoring), v) the level of financial support received from public authorities. Some Network institutes may face internal competition by other national institutions with overlapping responsabilities, which may impede their capacity to locally lead field actions.

• **The stability of the scientific staff in some Network institutes is fragile** and can be seriously compromised by a lack of important local resource which, in the context of weak staff development, hampers the capacity of that institute to participate to international collaborative projects.

• The access to the Network's technological resources and databases and the easy exchange of biological material are key determinants to the success of the transversal programmes but are still **poorly clarified and need legal formalisation.**

• **Epidemiology** is at the heart of the Network Public Health missions but is unequally represented in the Network. Not all of the institutes have an epidemiology department with a sufficient number of trained specialists, particularly in modelling. This is a priority area that needs reinforcing.

• The relations of the Network institutes with **hospitals and with veterinary partners** of the Ministry of Agriculture are of variable quality and reliability, though they are key to the success of programmes requiring access to patients and to domestic animals. It would benefit the Network to establish an attractive framework for an extended partnership with hospitals and veterinary facilities to foster and motivate their participation in scientific programmes from the early stages.

• The Network activities still have a strong "human health" connotation. As for the veterinary/ecology component, there are **only few veterinarians; specialists in ecology and wild fauna studies are missing; lack of Social and Human Sciences (SHS) specialists, lack of competencies in socioeconomic studies.** Recruiting top experts in these fields or establishing a solid partnership with other international institutions/teams, active in these fields, is a priority to address these deficits.

• The Network's management and coordination tools should be well-tailored to the ambition set forth. We need to determine whether the **Pasteur International Network association** (PINa) as it stands today, is well-equipped for this ambition or whether its capacity should be strengthened to convince the major funding agencies of its ability to manage complex research, consortia-based programmes.

• Similarly, **an IPIN scientific steering committee** is still missing, and should be created to advise on cross-cutting network activities and priorities, and to monitor and evaluate the progress of collaborative programme.

OPPORTUNITIES

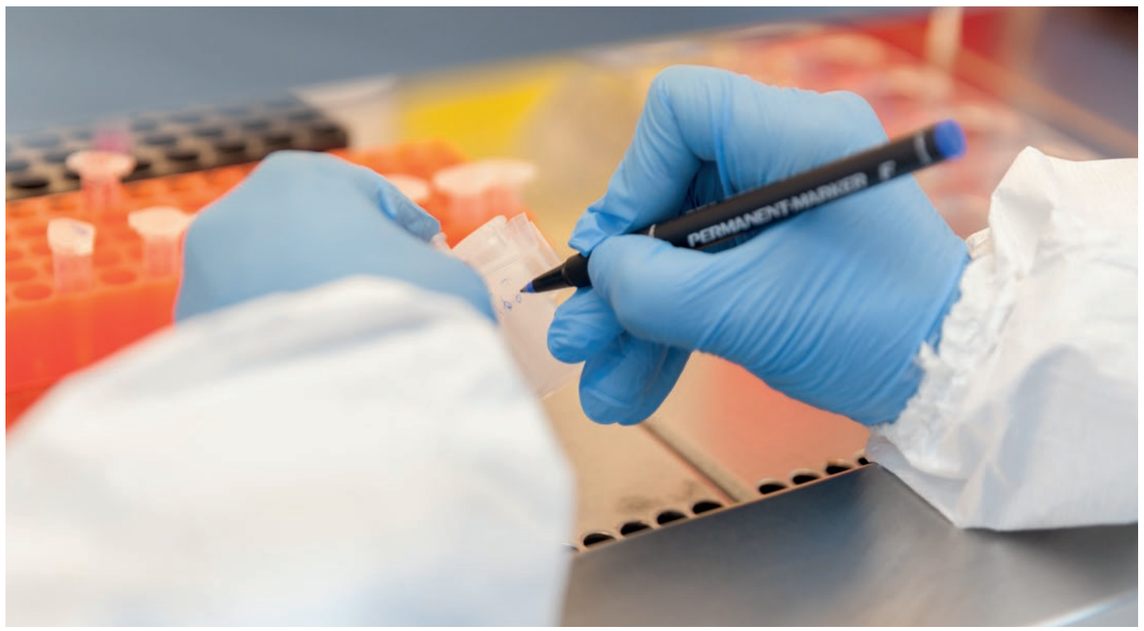
• IPs established in biodiveristy-rich countries have the opportunity to build in-country facilities (wild animal rearing and BSL2 and BSL3 insectariums) to study infectious cycles, conduct experiments on the transmission of infectious agents in local species of interest (endemic species particularly bats and rodents) and to conduct longitudinal studies on experimental or natural infections in wild reservoirs. Such studies which are crucial to understand the spillover/emergence phenomenon, would be impossible, or very difficult, to perform outside the countries of origin, for regulatory reasons.

THREATS

• The Network ambition to challenge and lead at a global level on relevant health issues is dependent on its capacity to develop **original approaches, based on new concepts, technological or operational advances, derived from its own research**. The risk would be for the Network to propose or undertake large formulaic projects that have no impact on the health of populations, or get involved in imitative projects that merely reproduce what is done elsewhere by other international stakeholders. This stresses the importance for the Network to hold high-level brainstorming meetings, guided by the question: to what extent is our action really original and innovative?

• The careful selection of the programme leaders of large multidisciplinary consortia is a crucial step. It needs to be governed by collective interest, addressing any difficulties that may appear through established and agreed equitable rules. An alternative approach to large consortia would be to split the set programme of actions (work packages) into multiple complementary subprogrammes conducted by smaller subconsortia. This approach may also help tailor the projected activities to the specificities of the different funding agencies according to their own priorities.

• Only relying on external funding for all the programme budget is risky. The success of a strategy depends on available funds, at least in the initial phases so as to leverage larger external funds. It is important that the Network members secure seed-funding to cover expenses during the initial phase.



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Which pertinent criteria should guide the selection of major joint actions?

The rationale of the global mobilisation of the Network is not just to make the network's programmes bigger (more data, etc.), but, more importantly, to improve the value of the collected data, improving the quality of the research, and taking full advantage of available diversity (genetic, socioeconomic, ecosystemic etc.) to which the Network gives access. Such diversities will determine differences in pathogen transmission, alter disease pattern, and potentially help researchers to further develop efficient preventive measures.

The implementation of a «problem-solving» approach requires brainstorming sessions to identify the bottlenecks that perpetuate the health problem at the global/regional level, and to specify the actions susceptible to relieve these bottlenecks.

The Network should therefore select a few global health challenges on which it can apply original concepts and solutions. Each research project should demonstrate how a partnership could be gauged at the network scale, and implemented across diverse ecosystems, and how it will generate real added value and improved outcomes than the "standard" partnership (i.e. reduced to two or three partners).

Technological research is at the heart of the action to develop effective diagnostic tools, especially Point-of-Care tests, aimed at the most marginal populations. Basic research is needed where new knowledge is required for solving identified problems. Otherwise, this type of research is more adapted to small partnerships among research teams that co-opt each other. Still, it can benefit from the outcomes of said projects.

Based on these considerations, the following table states the key questions to evaluate the quality of a project.

THE TARGETED HEALTH CHALLENGE

Is it globally distributed and does it generate a high mortality or morbidity?

Is it considered a priority at an international level?

Is there a large deficit in healthcare information or knowledge related to the targeted problem?

Are the bottlenecks that account for the persistence of the problem identified?

Are the solutions to remove these bottlenecks identified and affordable?

THE MOBILISED PARTNERSHIP

What are the assets that put the Network in a better position within the international competition to conduct this research?

Is the partnership based on true complementarity among the members?

Has the project identified international partners (outside the Network) capable of contributing to its visibility?

THE RESEARCH PROGRAMME TO BE DEVELOPED

Is it based on a new approach to the problem in light of new concepts and knowledge and/or new methodologies?

Is it innovative in terms of development of tangible outcomes?

Is the approach multidisciplinary, interdisciplinary, multisectorial?

Does it take advantage of the geographic advantages of the network and is there a scientific benefit from that?

Does the project involve the development of specific tools?

Are biobanking and data sharing dimensions taken into account?

Does the project have an interventional component?

THE EXPECTED OUTCOMES OF THE PROGRAMME

Will the project generate new and/or missing knowledge on the epidemiology of the disease, the risk factors and the characteristics of the populations exposed to these risks?

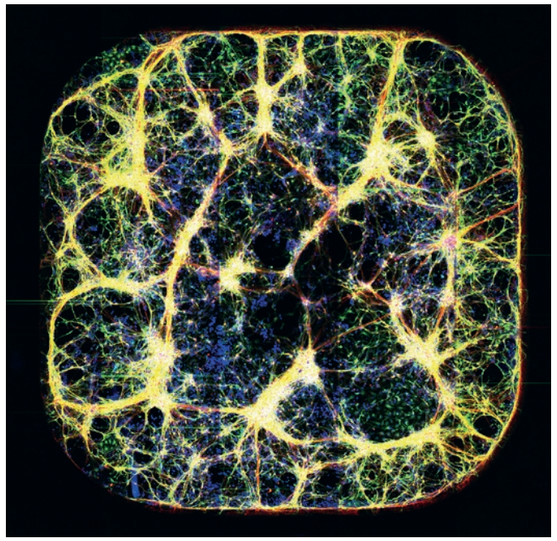
Will it finally have a significant impact on the reduction of risks for the exposed populations?

Will the project generate big data and is there a true data sharing?

Will it have a capacity-building component particularly at the master, doctoral, and postdoctoral degrees?

Will it lead to standardisation of practice between the participating institutes?

How does the project contribute to reinforcing the scientific and technological capacities of the Network member partners in terms of a possible transfer of technologies in the context of the project?



Scientific priorities

1
Priority research strands for the Network's programmes.

2
Which emblematic diseases should the Network target within these priority areas?

1

Priority research strands for the Network's programmes

Four priority areas were identified by the scientifc steering committee, and endorsed by IPIN's board of directors during its 49th session.

1 - Implementation of a "One Health" approach to explore the main zoonoses.

- Studies targeting the pathogens, their vectors (if any), their human host, their domestic and wild animal reservoirs evolving in their natural or anthropized ecosystems, in order to understand the mechanism of endemic persistence or the emergence of human infection and the role of human activities, as to shed light on preventive measures.

- Comparative studies in different regional groups of the Network, of infectious agents that cause febrile diseases as well as the various clinical syndromes, to specify the respective significance of known or unknown microbial, viral and parasitic pathogens, to draw a map of exposure profiles across the different participating countries, and to capture in real time and space the changes in their impact on the health of populations on the background of the pressures on ecosystems due to anthropogenic (e.g.: urbanisation, deforestation, hydraulic works) and non-anthropogenic (climatic) factors.

- The same goes for Network-wide monitoring of resistance to anti-infectious agents: antibiotics (Staphylococci, enterococci, E. coli, Salmonella, Klebsiella and other hospital microbes), anti-tuberculosis agents (M. tuberculosis), antiviral agents (HIV), antiparasitic agents (malaria, leishmaniasis)

- Special interest is to be paid to emerging viruses (Nipah, SARS, MERS, Ebola, Lassa, etc.), screened in their putative reservoirs, and mapped across the diverse ecosystems, to assess their distribution beyond their initial zones of emergence, and to potentially identify in these areas viruses phylogenetically related to the prototypical emerging viruses, which might themselves emerge in human populations one day.

- More generally, Next-Generation Sequencing (NGS) studies of infectious agents in wild fauna and vectors (mosquitos, ticks) and testing their capacity to cross the species barrier leading to asymptomatic or short lived spillover in humans living in close contact with the wild fauna (serology, fever monitoring in children). These studies may help identifying candidates for potential infectious emergence in the future.

2 - Investigation of vector-borne infectious diseases

With special focus on the biology of vectors, their genetic diversity, the natural history of the infection in humans, according to individual factors (genetic, epigenetic, ecosystemic, comorbidities), the dynamics and conditions of endemisation process in newly invaded territories, functional studies on pathogen-vector interactions, and the factors that interfere with vectorial competence and their temporal and spatial distribution; exploration of vector-borne diseases under intense vector control pressure, and identification of escape or perpetuation processes of a silent transmission, development of innovative vector control strategies more environmentally friendly.

3 - Exploring Mother-Child Health and childhood health issues

Especially in countries with high demographic growth or limited resources, with significant exposed/fragilised minorities and other vulnerable groups (immigrants).

1) infections during **pregnancy** and their impact on foetal mortality and foetal malformations,

2) sepsis during the **perinatal period**,

3) impact of malnutrition and bad living conditions on respiratory infections, diarrhoea and meningo-encephalitis in **childhood,**

4) special health risks associated with **adolescence.**

The Network has the unique capacity to generate on a regular basis snapshots on infant population health, particularly in terms of risk of infection that encompass a diversity of contributing factors. These snapshots generated in a coordinated manner over the vast territories covered by the Network, and undertaken at regular intervals (7-10 years), would enable us to establish and consolidate a set of health indicators on the actual risks, to which these highly sensitive age groups are exposed, and the dynamics of changes that may occur over time as a consequence of epidemiological transition, changes in living conditions and environmental parameters (including sanitary conditions and climate change), as well as in care delivery.

4 - Studying the impact of ageing/ longevity on health, including chronic diseases

(Metabolic syndrome, cancer, genetic diseases, inflammatory diseases, neurodegenerative diseases). The increasing burden of these chronic diseases and their determinants in the context of the epidemiological transition, which are occuring in almost all countries of the Network, and with a special emphasis on the putative role played by infectious agents and “biota” on these chronic diseases.

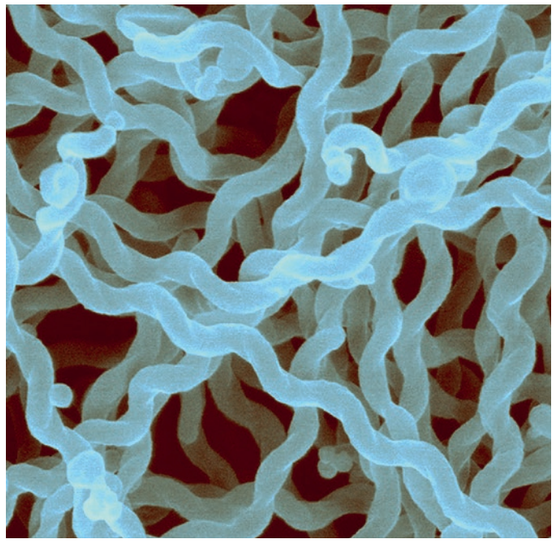
2

Which emblematic diseases should the Network target within these priority areas?

Disease targets along the priority areas were discussed, and ten infectious diseases emerged as priorities from the debates: In order of decreasing priority, they are: **Rabies, leptospirosis, malaria, tuberculosis, leishmaniasis, resistance to antimicrobial agents, dengue, Buruli ulcer, brucellosis, hepatitis.** Most are zoonoses and neglected tropical diseases, two of which (leptospirosis and brucellosis) are comparatively much less studied on an international level. Three diseases (malaria, dengue and leishmaniasis) are emblematic vector-borne diseases and one target (antimicrobial resistance) represents a cross-sectional health issue. With regard to noncommunicable diseases and impact of ageing, it was recognised that only few IP in the Network, primarily in Europe (Paris, Lille, Rome and Athens), invest in these fields. A compromise might be to focus collaborative efforts on the determinants of chronic diseases that fit with the available expertise: Impact of the genetic diversity; the microbiota as an adjuvant sensitive to the living environment; virus and cancer, infectious diseases with neurological impact (acute, subacute and chronic encephalitis); inflammation in non transmissible diseases. One should mention a few serious environmental risk factors with a strong regional nature: ophidian and scorpion envenomation. The basic research associated with these issues may pave the way to the identification of new toxic and/or pharmacologically active substances contained in venoms.

An online consultation was launched in early 2017 to collect feedback across the Pasteur community on what should be the Network's priorities. An online questionnaire with 39 questions was developed and distributed across the Pasteur community. The results of this online consultation, which was the first of its type conducted in the Network, are summarised below. By 15 February 2017, a total of 665 people connected to the online questionnaire, with 213 (32%) Pasteurian colleagues completing the forms. One third of the respondents were affiliated with IP Paris and two thirds with 28 network institutes. There was no difference between the responses from the IP scientists and those from the other Network institutes.

Overall, the consultation revealed a clear demand for more collaboration, improved functional integration of Institutes within a true network, and for more opportunities for interaction among Network scientists. A large majority of respondents (82%) agreed on the importance of keeping up Network meetings organized at the regional level. A large majority (80%) also agreed with the five priority areas proposed for transversal research programmes by the scientifc steering committee. However, to the question of prioritizing the target diseases, the respondents listed, in decreasing order of priority: Antimicrobial resistance (AMR), Tuberculosis, Malaria, Dengue, Hepatitis, Rabies, Leishmaniasis, Leptospirosis, Brucellosis and Buruli Ulcer. Close to 80% of the respondents agreed that the IPIN should extend their research activities to non-communicable diseases, and identified them, in decreasing order of priority, as follows: cancer, genetic disorders, neurodegenerative diseases, and metabolic syndrome. When asked about their priority needs in terms of tools, training, and expertise for their clinical research and studies, **bioinformatics, biostatistics and next generation sequencing**, including access to technology platforms, were identified as priorities.



The results of the consultation were discussed at a feedback meeting held on 15 February 2017, attended by six members of the SCS. In contrast to the recommendation of the SCSS, the five diseases chosen as a priority by the Network scientists **(malaria, dengue, AMR, tuberculosis, hepatitis)** are major pathologies already targeted and well-funded by the international community, and the Network is already quite committed and active in these areas as is demonstrated by a significant scientific production. For these model pathologies, the Network could invest in more cross-disciplinary partnerships and better integration of actions.

Network scientists pushed back on previously identified priority areas such as **rabies, leishmaniasis, leptospirosis, brucellosis and Buruli Ulcer.** These diseases (at least the first four) are, in terms of morbidity and mortality, just as important on an international level, but they represent **niches** where the Network institutes invested less in research and scientific production so far. The participants acknowledged that Rabies is a special case due to the **investment of** the Network institutes in vaccination centers and national reference centers **and this disease** has a strong symbolic link with the Network. Leishmaniasis is also studied in many institutes and the network has the LeiSHield project which is quite active in this field. **Leptospirosis** is a neglected zoonosis studied by a few Network institutes and a model for integration in the One Health concept but it remains quite unknown and underestimated in terms of the extent of the problem. There is an urgent need to evaluate the morbidity and mortality burden of this disease, and to conduct wide-ranging field research to understand the level of Leptospira diversity and its adaptation to reservoir animals across diverse ecosystems, and to generate control measures which are entirely absent today. For **Brucellosis**, only one institute is working on this subject, which excludes it from the selection criteria cited above. For **Buruli Ulcer**, the research interest of this mycobacterium is counterbalanced by the decline in the number of cases even in Cameroon, a country where the morbidity burden of the disease was historically the highest.

The result of the consultation clearly poses the question of the pertinent choice of models in which the Network should invest: niches or classic major pathologies? The choice will also be dictated by the potential for collaboration and cross-disciplinary integration generated among the institutes.

Rather than a choice in principle, it is in fact the methodology of the action that is important: a brainstorming session between Network players and external experts is crucially required to discuss each healthcare challenge with regards to the specificity and innovative capacity of the Network approches. To begin with, rabies, tuberculosis, antimicrobial resistance, hepatitis, and leptospirosis are suggested for this exercise.

Recommandations for the future

1
How should the Network research programmes be coordinated at the local, regional and international levels?

2
Which actions should prepare the Network to confront future epidemic crises?

3
Which structures and activities support the globalised ambition of the Network?

1

How should the Network research programmes be coordinated at the local, regional and international levels?

Synergy and convergence on few priorities will only materialise if Network members are seriously convinced that closer interconnection serves the Network, and therefore, their own interests. Hence, the proposed common strategy must be congruent with the institutional strategies of individual member institutes.

Participation in the extended partnerships within the Network is left to the free decision of each institute. The optimal consortium size is mainly determined by the geographic distribution of the targeted health challenge, the diversity levels to be explored, and the envisaged activity. An extensive rabies programme could target three Pasteur regions out of five: Asia, Sub-Saharan Africa, and MATI. A programme on leptospirosis might interest the five geographical regions. An Antimicrobial Resistance programme could involve all the Network institutes for data collection and analysis. A programme on infection ecology or emerging diseases could enlist population (or patient) cohorts exposed to interfaces with wild fauna, particularly in biodiversity hotspots.

The Network Research programmes would clearly gain from being **integrated at the regional level:** Endemic infections are largely determined by eco-climatic, socioeconomic, and cultural conditions, which are regionally shared factors, and the epidemic spread primarily occurs at the local and regional levels. The regional structure of the Network, established since the beginning of the 2000s, addresses this reality, and is not contradictory to the global ambition of the Network programmes.

2

Which actions should prepare the Network to confront future epidemic crises?

During outbreak events, member(s) of the Network may have two important roles to play: i) they can be solicited to provide assistance to a member IP or to a third party State to investigate a threatening epidemic and help to identifying the causal agent, ii) they can also contribute to generate and participate to research programmes.

Beyond the mere characterisation of the respective pathogen(s), outbreaks offer the opportunity to adress **research questions, which are specific to the epidemic phase,** the sort of questions that are inaccessible to exploration during the post- or inter-epidemic phases; for instance, i) to describe the full clinical spectrum of disease, and to unveil rare complications that emerge, because of the high number of cases generated when an epidemic strikes a naive population; ii) to detect molecular evolutions of pathogen during the epidemic that may induce a change in the host response, or increase the virulence of the pathogen; iv) to decode mechanisms of contamination that could guide the implementation of preventive interventions.

In the context of an outbreak situation, research teams are challenged to rapidly establish research programme(s) in a race against the clock while the epidemic is still in progress: formulating pertinent research questions, bringing together researchers from the country of emergence and from elsewhere, obtaining ethics committee approvals, and finding the financial resources; all procedures that must be conducted in the emergency before the epidemic will decline and eventually end. This requires a high level of responsiveness and connectivity, pre-identified procedures, accelerated decision circuits, and funding mobilisation.

The Network should deliberate on how to take on the research component in the pre-epidemic phase and discuss the creation of a joint emergency fund, fed by an annual contribution of the Network members, and looked after by PINa. This fund will be dispensed by the IPIN Board of directors in the event of an emergency to the relevant Network institutes to support research activities and interventions.

Epidemics are key events for IPs, especially when they cause high morbidity and/or mortality. During these dramatic moments when **the Pasteur institutions commit their resources,** they are at the forefront to help health authorities to confront the emergency, and **it is important to prepare for these occasions before they occur.**

With that objective in mind, IP Paris has structured two teams that can be mobilised in emergency situations: the **CIBU**, a biological emergency intervention unit, devoted to identifying the responsible pathogen(s) as quickly as possible, and **the Outbreak Investigation Task Force** whose role is to assist local authorities to collect and analyse microbiological and epidemiological data as soon as possible, and to pave the way to associated research projects.

In order to foster a stronger involvement of the Network in these commendable efforts, the following actions are recommended:

• To mobilise with the IP Paris teams the competencies of other institutes, especially those that have acquired experience in this field, Institut Pasteur de Dakar, Institut Pasteur Korea, Hong Kong University-Pasteur Research Pole, etc...

• To identify in each institute of the Network, an "Outbreak Investigations" focal point (or even a team). This focal point will be the local link for the seemless sharing of all information related to the management of epidemic crises.

• It is advisable for each institute to document the legal (statutory) responsibility delegated by its supervisory authority as to the precise role they are able to play in case of an epidemic crisis, and to ensure that any ambiguity or overlap with other local institution(s) be removed or clarified.

• The expertise in the field of epidemiology, and intervention of teams locally engaged in outbreak monitoring, must be maintained over the long term. The special training courses on the theoretical and practical issues of an Outbreak Investigation should be made available across the Network, combined with the implementation of a manual of procedures.

• The CIBU should coordinate any activities within the Network to identify the optimal list of diagnostic tests best adapted to the main local/regional context, and to conduct proficiency tests to carry out targeted microbiological monitoring and rapid intervention during outbreak.

3

Which structures and activities support the globalised ambition of the Network?

Several technological platforms developed at IP are valuable resources for the Network to run the collaborative programmes.

• **The Resources and technologicale research center C2RT** functions as a technological hub to develop, provide access to, and share high-technology equipment and methods, competences and training (electron microscopy, imaging, genome platforms, transcriptomics, epigenetic analysis, proteomics, crystallography, antibody engineering, recombinant proteins, experimental breeding farm, insectarium, etc.)

• **The Biological Resource Center of Institut PCRBPI** is aimed at harmonising, optimising, and upgrading the collections of microorganisms and methods of analysis within the expert laboratories in Paris and in the Network. PIBnet involves the National Reference Centres and the WHO Collaborating Centres, the Biological Resources Centres and the Emergency Biological Intervention Unit already mentioned above. A shared microbiology platform was established. The characterisation of isolates is done by sequencing and genotyping techniques, transcriptomics, and metabolomics.

• **The Department of Computational Biology** regroups scientific teams specialised in these three fields in very diverse research sectors (human evolutionary genetics, microbe evolutionary genomics, spatial genome regulation, evolutionary bioinformatics, statistical genetics, systems biology; structural bioinformatics; human genetics and cognitive functions; mathematical epidemiology; imaging and modelling). Through their **bioinformatics platform**, they offer assistance to analyse data collected by network third party teams.

• **The Centre for Translational Research (CRT)** helps the Institut Pasteur and Network researchers to undertake **translational research projects**, design and develop clinical studies and formalise ethical and regulatory steps. It provides access to a technological platform that is adapted to the needs of programmes

as well as to the resources of a biobank of specimens from healthy individuals and patients.

A few complementary actions are suggested to improve the functional connectivity of the Network:

• To identify the advanced technological resources and platforms ***located in other institutes of the network*** (Lille, Korea, Cayenne, Montevideo, etc), which may be made accessible to the entire Pasteur community.

• At the network level, to define the rules and conditions for accessing shared resources and platforms, and their contractual nature. (For example: scientific partnership activity or technological assistance activity? Free of charge or paid service? Restricted to bilateral or multilateral projects or accessible to the specific programmes of network members teams?

• Considering the Network's global ambition, it is advisable to conduct an evaluation of the conditions under which **laboratory animals are raised or kept in Network animal facilities,** and to advise institutes to align these structures with intenationally recognised standards in order to maintain the quality of animal experimentation.

• An expert committee should ***define the typology of the expertise*** available/required at different levels of the Network.

> Expertise to be implemented at the local level that corresponds to recurrent skills required to the official missions of the institution: microbiological monitoring; reference laboratories; epidemiology and outbreak investigation …

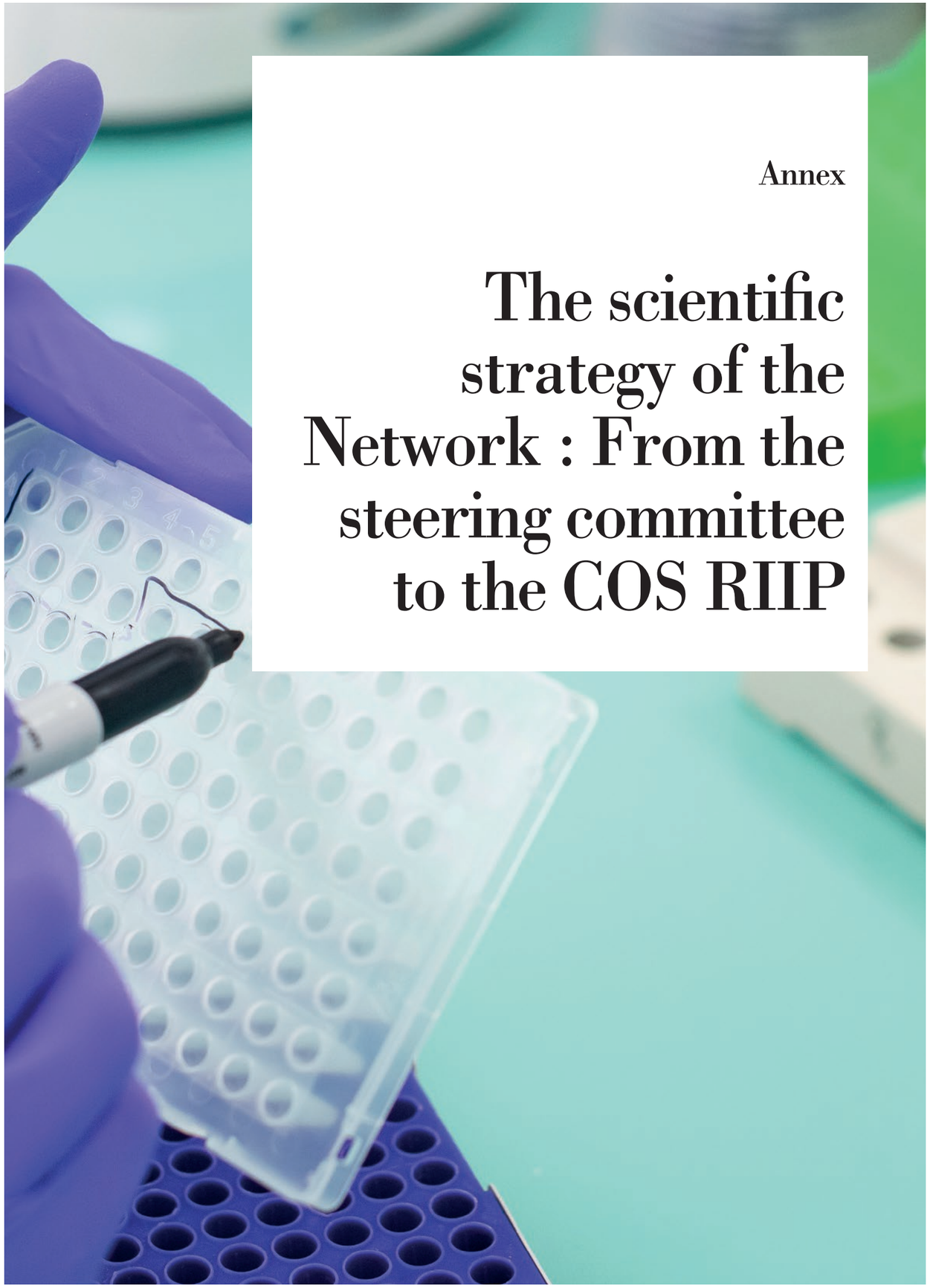
> Expertise to be implemented at the regional level at secondary hubs, more associated with specific research programmes or restricted by scarce human resources (bioinformatics platforms, sequencing facilities).

> Expertise requiring highly specialised competences, and/or high-technology equipment. This expertise might be recruited from Network members where it is available.

• A commendable policy was initiated for few, many or a couple of (TBD) years now, aiming at the **coordinated development of biobanks in the Network's institutes.** In order to ensure interoperability, it is crucial that the Network produce standardised technical and legal reference document(s) on how to manage the collection, conservation of specimens, and distribution of biological samples of animal or human origin including issues pertaining to biosafety, ethics, and intellectual property.

• At the heart of the partnership within IPIN is **the need for training**. This demand is a constant, regardless of the country development level, and must be considered as an absolute priority for the Network: academic-type training at the master, doctoral/ postdoctoral level, continuing vocational training, training in new technologies and methodologies, training in biosafety rules, in quality assurance, in tools validation, training of medical biologists such as those involved in microbiological reference activities.

An extremely diversified portfolio of theoretical and practical courses was developed at the Institut Pasteur in Paris and in the Network institutes that have required heavy investment and dedicated skills. These courses should be further developed by making them accesible to the Network institutes. **The creation of an international standards label should be considered in the frame of an "International Pasteur School in Biosciences" or an "International Pasteur Courses in Biosciences".** This label will be attributed only to courses delivered by the Network members according to defined selection criteria. It will guarantee the quality of training for students attending the courses, and will value the support provided by the institutes to the doctoral schools in the host countries. More generally, it will offer greater visibility and recognition of the training offered across the Network in biosciences to the international science community, especially for universities and research centres in Anglophone countries. This initiative is perfectly in keeping with the Network's international ambition.



Annex

The scientific strategy of the Network : From the steering committee to the COS RIIP

Warm thanks to all the Institut Pasteur International Network directors, who actively contributed to the development of the Network's scientific strategy fromits inception in June 2016, at the Château des Ravatys, to its validation at the 49th Directors' Meeting in Abidjan. This streering committee was composed of the following members :

- **Luis Barbeito,** Institut Pasteur de Montevideo
- **Patrick Berche,** Institut Pasteur de Lille (excused)
- **Saeid Bouzari,** Institut Pasteur in Iran
- **Didier Fontenille,** Institut Pasteur du Cambodge
- **Mirdad Kazanji,** Institut Pasteur de la Guyane
- **Hechmi Louzir,** Institut Pasteur de Tunis
- **Voahangui Rasolofo,** Institut Pasteur de Madagascar
- **Angela Santoni,** Institut Pasteur in Italy – Cenci Bolognetti Foundation
- **Noël Tordo,** Institut Pasteur de Guinée

- **Koussay Dellagi,** Department of International affairs (rapporteur)
- **Arnaud Fontanet,** Center for Global Health
- **Marc Jouan,** Department of International affairs
- **Antonio Borderia,** Department of International affairs
- **Rebecca Grant,** Center for Global Health

OBJECTIVES OF THE STEERING COMMITTEE

To define a shared vision of global health challenges and the scientific strategy that would mobilise the Network as a coordinated scientific body to face a few healthcare challenges for which the Network aspires to become world leader.

Other specific objectives :

- To identify by a SWOT analysis, the strengths which support the network's ambition and the weaknesses to be addressed.
- To define the priority areas of research and intervention that benefit from these strengths.
- To specify the network's mobilisation instruments.
- To define the governance structure, best suited to monitor the strategy of implementation, and for running major Network cooperative programmes.
- To propose a method for writing the programmes that will be agreed on.

We warmly thank the entire scientific community of the Network who participated in establishing the research priorities and axes likely to consolidate links between members of the IPIN, and until the creation of the COS RIIP in December 2018.

THE OBJECTIVE AND THE COMPOSITION OF THE COS RIIP

COS RIIP will have the major responsibility of finding on the means to bring out the COS RIIP as a major player in global health and to follow through the implementation of its major programs of action

It is composed as follow:

- **Anna-Bella Failloux,** Institut Pasteur, Paris – Chairwoman of the COS RIIP
- **Dominique Rousset,** Institut Pasteur de la Guyane
- **Mohamed-Ridha Barbouche,** Institut Pasteur de Tunis
- **Daniel A. Boakye,** Noguchi Memorial Institute for Medical Research, Accra, Ghana
- **Benoit Deprez,** Institut Pasteur de Lille
- **Peter Horby,** University of Oxford
- **Hein Min Tun,** Hong Kong University – Pasteur Research Pole
- **François Xavier Weill,** Institut Pasteur, Paris

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