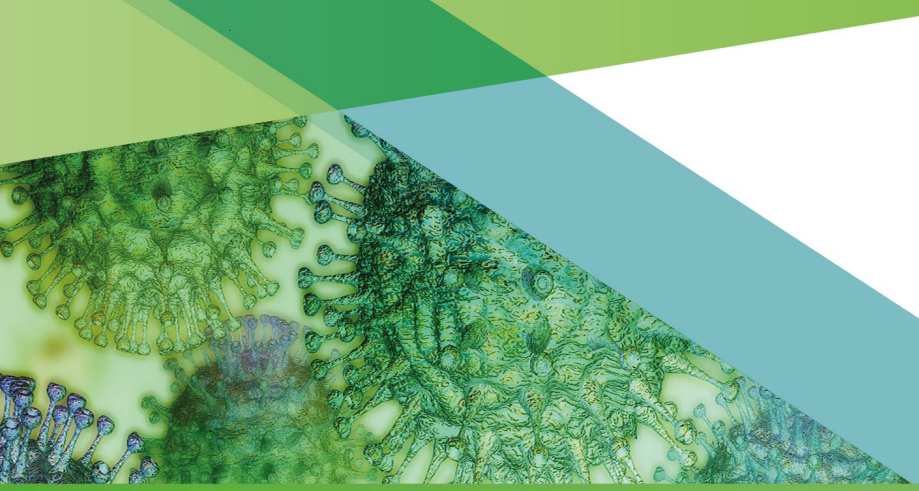

TECHNICAL REPORT

ECDC expert consultation on knowledge and research gaps related to the COVID-19 public health response

29 July 2022

Key facts

- In February 2022, after two years of the COVID-19 pandemic, the European Centre for Disease Prevention and Control (ECDC) undertook a consultation to identify knowledge and research gaps related to the COVID-19 public health response. The aim of this work was to inform future research activities that enhance the existing evidence base, support knowledge generation and synthesis, and reduce the level of policy uncertainty in addressing public health actions against COVID-19.
- A two-step qualitative process that utilised both internal and external expertise was used to identify and prioritise research gaps that remain pertinent for public health action at present and that may have increasing relevance to inform policy in the coming months, given the current trajectory of the pandemic in early 2022.
- Twenty-two high-level research gaps were identified during semi-structured interviews with internal ECDC expert groups from various COVID-19 domains. The 22 research gaps were consolidated and organised into three thematic areas; 'COVID-19 biology and the intersection with human host populations', 'Pandemic response: effectiveness of control measures and impact of behavioural, political and social context' and 'Pandemic (re-)emergence and new variants'.
- The research gaps under each thematic area were presented to the ECDC Advisory Forum, a group of senior EU/EEA representatives mandated to advise ECDC on scientific issues. Advisory Forum members ranked the research gaps within each thematic area using a predefined set of criteria to provide insight into the relative priority of each research gap and to inform future research action. Notably, each of the 22 research gaps received support as a high-priority area for further research from at least one Advisory Forum member. There was also consensus on the highest priority research gaps within each thematic area.
- Research gaps that were selected as one of the top three priorities in their thematic areas by 80% or more of the Advisory Forum members included: research to improve understandings of 'immunity and immune response', characterisation of the 'burden of disease' and overall clinical impact, 'the systematic evaluation of prevention and control measures' and 'novel surveillance and monitoring strategies'.

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Stockholm, July 2022

Scope of this document

ECDC is mandated to '*consult the Commission with regard to the planning and priority setting of research and public health studies*' [1].

In support of this, Strategic Objective 3 in ECDC's Multiannual Strategy 2021-2027 includes specific focus to

- 'identify and address key knowledge gaps and areas of uncertainty and develop new multidisciplinary approaches to prevent and control infectious diseases' (Action Area 3.1),
- 'collaborate with partners to address gaps and uncertainties that lie within the Centre's mandate and capacity' (Action Area 3.2),
- 'link up with relevant partners such as Directorates-General of the European Commission regarding knowledge gaps that need to be addressed by further research' (Action Area 3.2). [2]

To facilitate this, ECDC has undertaken a project to identify knowledge and research gaps related to the COVID-19 public health response. This work was undertaken in February 2022 after two years of the pandemic and sought to identify issues that remain pertinent for public health action and that may have increasing relevance to inform policy in the coming months given the trajectory of the pandemic in early 2022. This project is also a pilot for future approaches to identify and promote knowledge and research gaps with both internal and external experts in other disease areas.

The aim of this work was to inform future research activities that enhance the existing evidence base, support knowledge generation and synthesis, and reduce the level of policy uncertainty in addressing public health actions against COVID-19.

Target audience

This report is intended for ECDC and external stakeholders, including national and European Union (EU) level health policy leads and research funders (the Directorate-General for Health and Food Safety, the Directorate-General for Research and Innovation, European Health and Emergency Preparedness and response Authority, and other EU actors providing ongoing financial support for research action around COVID-19) [3].

Background

COVID-19 has dominated the public health agenda in the European Union (EU) and European Economic Area (EEA) for the past two years. During this time, there has been huge research investment directed at understanding all aspects of SARS-CoV-2 and the COVID-19 pandemic at global [4] and EU levels [3]. Substantial gains in knowledge have accrued from this investment. The global public health community has an ever-improving understanding of multiple aspects of COVID-19, from virology of SARS-CoV-2 and the evolving epidemiology and dynamics of the pandemic to intervention approaches, including the unprecedented development and roll-out of pandemic-specific vaccines, which continue to be the most effective tool to limit the health impacts of COVID-19.

However, areas of scientific uncertainty continue to undermine scientific advice and evidence-informed policy making in response to the evolving pandemic. Therefore, it is important that these knowledge gaps are identified so research can be tailored to improve the evidence base.

The knowledge gap identification conducted in this study included taking stock of the current evidence base and noting what knowledge gaps and scientific uncertainties have persisted after two years of the pandemic, as well as those that may arise in the coming months that might be amendable to research action. This assessment builds on a similar internally led exercise, undertaken 18 months earlier, to identify knowledge and research gaps for non-pharmaceutical interventions (NPIs). This led to the publication of a paper summarising the research gaps that reduced policy certainty around the effectiveness of such mitigation measures at that time [5]. However, the scope was relatively narrow, and this review takes a wider focus covering other domains of the COVID-19 response.

Methods

Identification of knowledge and research gaps

A qualitative, semi-structured group interview methodology was used to collect the opinions of ECDC experts on knowledge and research gaps within eight different topic domains related to the COVID-19 public health response. Groups were chosen based on pre-existing structures within ECDC's Public Health Emergency (PHE) and COVID-19 response activities, and to reflect the different areas of technical responsibility. Each group offered detailed expertise and understanding of the existing knowledge base in their areas of responsibility, informed by ongoing appraisal and synthesis of the evolving evidence base and regular consultation with public health professionals in EU/EEA countries. The consulted experts were therefore well suited to provide an overview of current scientific uncertainty and knowledge shortfalls in each technical domain, as well as knowledge needs that may inform future policy action given the current state of the COVID-19 pandemic and its trajectory.

One-hour meetings were arranged with each group in the week beginning 31 January 2022. The ECDC Research Coordinator who led the process, started each meeting by presenting a short introduction of the project. Participants were also advised that the discussion should be framed by the following aims and scope. These were also shared in advance of each meeting.

Aims

The aims of the exercise were to:

- capture and review existing knowledge gaps related to SARS-CoV-2 and the COVID-19 public health response, within the context of the various technical areas under ECDC's mandate,
- inform decisions on the prioritisation and allocation of research resources to address the current situation, and
- identify research necessary to inform the 'new normal' (i.e. pre-emptive research that could be undertaken now to reduce future policy uncertainty, given the current trajectory of the pandemic).

Scope

The scope of the exercise comprised the following:

- The focus of the exercise was on identifying and assessing knowledge gaps relevant to immediate and longer-term policy actions, including interventions, preparedness, modelling inputs and public health actions.
- The resulting output would focus on informing decisions related to research starting months or years in the future.
- The primary audience for the output is EU research funders, but the output should also be of relevance to ECDC work plans, national public health institutes and national funders.

Knowledge gaps and research priority proposals were considered out of scope if they related to:

- research targeting immediate actions (epidemiological characterisation, virological typing etc.) or
- internal operations (e.g. priorities/actions arising from after-action review of ECDC activities).

Interview questions

After the introduction, groups were asked to consider four key questions during a semi-moderated discussion, with specific focus on the current and future knowledge and research gaps in each respective domain. The four key questions were:

- **What:** Based on your knowledge of COVID-19 to date, what are the most important or relevant scientific/public health uncertainties and knowledge gaps that persist today (up to three)?
- **Why:** For each identified gap, why is this important? Describe how acquiring this knowledge would facilitate public health understanding or action.
- **How:** What research is needed to address the identified knowledge gaps? What studies, methods or scientific approaches could facilitate acquiring this knowledge?
- **Future:** Given the current direction of the COVID-19 pandemic, and current and future options for response, which of the identified knowledge gaps may need to be addressed with greater urgency in the next six months, compared with the current priorities.

All points made during the discussions were recorded. To close each session, moderators shared detailed written summary notes and two or three of the highest priority knowledge and research gaps identified during the meeting with the group for verification.

Assimilation and prioritisation of identified knowledge and research gaps

Following completion of the interviews, the lead investigators conducted a consolidation and grouping exercise to place the identified priorities into a structure that was suitable for further review and prioritisation. The identified knowledge and research gaps were divided into three thematic areas. The results were presented to the ECDC Advisory Forum in February 2022. The Advisory Forum is a mandated governance body (defined in ECDC's Founding Regulation [1]) comprised of representatives designated by each Member State. Advisory Forum members, recognised for their scientific competence, advise ECDC on the quality of scientific work undertaken by the Centre and ensure close cooperation between the Centre and the competent bodies in the Member States. For this study, Advisory Forum input ensured that senior representatives of EU/EEA national public health institutes and agencies – and other appointed partner organisations – were able to verify the scientific validity of the knowledge gaps collected and highlight any obvious omissions.

The Advisory Forum also undertook a ranking exercise to identify if there was consensus on which knowledge gaps should be pursued with high priority. Input was given during a virtual meeting using an online selection tool. Each member gave their view independently, anonymously and in real time. The aggregate ranking results were only presented upon completion of each ranking exercise, so participants had no knowledge of priorities proposed by others during the exercise.

In accordance with Advisory Forum procedure, attending Advisory Forum members representing EU/EEA countries were eligible to perform the ranking exercise. Of the 30 EU/EEA countries represented in the Advisory Forum, 16 members were in attendance and eligible to participate. The ranking exercise used the IRIS approach[6]. IRIS is an ECDC-developed framework based on four pre-defined criteria (issue, resource, impact and solidarity) to support strategic prioritisation. The IRIS framework was used because Advisory Forum members are familiar with it and it can be used to prioritise activities in an EU context.

Advisory Forum members were asked to consider the identified knowledge and research gaps in each of the three thematic areas independently. They were then asked to select up to three gaps in each area that should, in their opinion, have the highest priority based on the adjusted IRIS criteria.

Adjusted IRIS criteria

The IRIS criteria were adjusted to suit the context of this study, as follows:

- Issue: The knowledge gap is relevant for European public health and requires collective engagement.
- Resource: The likely resource implications (research funding costs and necessary contribution from health or other sectors, i.e. opportunity costs) are justified by the potential benefits of research to address the knowledge gap.
- Impact: Addressing the knowledge gap is feasible and has the potential to make a difference and ultimately protect or improve population health in Europe, within an appropriate timescale (medium-long term: ≥9-12 months).
- Solidarity: Research to address the knowledge gap has the potential to reduce variances in health outcomes caused by public health inequalities in Europe.

Results

Primary knowledge gaps identified

Upon completion of the interviews with all eight technical groups of ECDC experts, a total of 22 high-level knowledge gaps were identified (Annex 1).

Consolidation and prioritisation of knowledge and research gaps

All eight group interviews identified specific knowledge and research gaps, but there was some overlap and common themes emerged. To support the Advisory Forum's assessment regarding prioritisation, the lead investigators conducted a consolidation exercise to group the list of knowledge gaps into three thematic areas:

- COVID-19 biology and the intersection with human host populations.
- Pandemic response: effectiveness of control measures and impact of behavioural, political and social context.
- Pandemic (re-)emergence and new variants.

The knowledge gaps in each thematic area and the 'Ranking ratio' awarded to each are presented in Tables 1-3. The Ranking ratio is the percentage of Advisory Forum members who selected a given research gap as one of their three high-priority gaps. The knowledge gaps are presented according to rank, in descending order.

COVID-19 biology and the intersection with human host populations

The research and knowledge gaps in this thematic area focus on understanding the basic virology of SARS-CoV-2 and on how the virus interacts with human hosts on individual and population levels (Table 1). These topics are vital for designing more targeted and effective policy responses and interventions in the future.

Table 1. Research gaps related to COVID-19 biology and the intersection with human host populations

Ranking	Knowledge and Research gap	Advisory Forum count (N = 15)	Ranking ratio*
1	**Immunity and immune response** to SARS-CoV-2, including the role in infection and clinical outcome (e.g. severe disease, death, transmission and post COVID-19 condition), duration of protective immunity, waning immunity, etc.	14	93%
2	The **burden of disease spectrum** of COVID-19, including calculation of disability-adjusted life years (DALYs) for post COVID condition and impacts of the presence of co-infection and existing (chronic) co-morbidities	12	80%
3	Characterisation of SARS-CoV-2, with a focus on understanding the **biological mechanisms of transmissibility and severity**	7	47%
4	Social mixing patterns and physical **contact pattern data** (e.g. behavioural insights, human contact patterns and effectiveness of non-pharmaceutical measures)	6	40%
5	**Healthcare-associated SARS-CoV-2 infections** (e.g. modes of transmission in healthcare settings, effectiveness of mitigation efforts and impact on patients and services).	5	33%

* *Ranking ratio: Percentage of Advisory Forum members who selected this research gap as one of their three high-priority gaps*

Pandemic response: effectiveness of control measures and impact of behavioural, political and social context

The knowledge and research gaps in this thematic area focus on understanding what the optimal response would look like in a (future) pandemic setting (Table 2). The focus is on evaluating – and designing new methods to evaluate – infection prevention and control (IPC) measures for their effectiveness at reaching certain public health goals, and on taking the often neglected yet vital behavioural, political and social components of any IPC measure or holistic pandemic response strategy into account.

Table 2. Research gaps related to pandemic response: effectiveness of control measures and impact of behavioural, political and social context

Ranking	Knowledge and Research gap	Advisory Forum count (N = 15)	Ranking ratio*
1	**Systematic evaluation of prevention and control measures** (testing, vaccination, social distancing, personal protective equipment, etc., and interplay between measures), as well as effectiveness, cost-effectiveness analysis and acceptability from a behavioural and social perspective	12	80%
2	Evaluation of public health (and economic) **losses or setbacks related to other infectious and non-infectious diseases** during the COVID-19 pandemic, and approaches to effectively re-address the balance (e.g. comparative burden and cost-effectiveness analysis)	10	67%
3	**Political, behavioural and social science research** (e.g. into behavioural, cultural and societal drivers that facilitate or inhibit population acceptance/adherence to public health interventions) and new methods to support comparative insight into behaviours during a pandemic	7	47%
=4	Vaccine formulation and the development of **new vaccines and therapeutics against SARS-CoV-2**	4	27%
=4	Improving **methods to investigate the effectiveness of public health and infection prevention and control interventions** both in a pandemic crisis setting and outside of one	4	27%
=6	**Operational research into ventilation systems** and real world assessment of the effectiveness of different types of ventilation and air filtering/cleaning (e.g. optimal placement and use)	3	20%
=6	The perspectives and needs of socially and medically **vulnerable groups** in policies and interventions	3	20%
=8	The impacts of a pandemic on the **healthcare workforce** and how to improve resilience and reduce direct and indirect health consequences from sustained periods of frontline action	1	7%
=8	**Implementation science and evidence regarding the use of decision frameworks** to optimise the application of knowledge in developing and implementing policies	1	7%

** Ranking ratio: Percentage of Advisory Forum members who selected this research gap as one of their three high-priority gaps*

Pandemic (re-)emergence and new variants

This thematic area covers identified research gaps that would improve understanding of the emergence of new variants of SARS-CoV-2 and other pathogens with pandemic potential (Table 3). The suggestions focus on how to better target surveillance for emerging threats and improve early identification and verification of risk in support of earlier decision-making to limit spread and impact.

Table 3. Pandemic (re-)emergence and new variants

Ranking	Knowledge and Research gap	Advisory Forum score (N=16)	Ranking ratio*
1	**Novel surveillance and monitoring strategies** (e.g. seroprevalence monitoring, waste water monitoring and bioinformatics), including translational research to integrate monitoring methods into coherent systems	14	88%
2	Optimising **public health responses to prevent or mitigate a new pandemic** (e.g. response strategy, human resources, contact tracing and understanding the breaking of contact chains)	11	69%
3	Methods to **rapidly characterise human host populations** to support interpretation of severity of new strains, taking into consideration demographics (e.g. age and sex), general health status, COVID-19 immunity status, past exposure to other pathogens, healthcare, geography, etc.	8	50%
=4	Defining costs/benefits and optimising global and European **data access, integration and data system approaches** to support timely data linkage and analysis of clinical, genomic and epidemiological data	5	31%
=4	**Understanding pandemic emergence**, including research into drivers of viral evolution	5	31%
6	**Genetic characterisation** (e.g. methods to predict and interpret antigenic drift/shift) and public health impact (e.g. transmissibility, severity, and immune and vaccine escape)	3	19%
7	**Monitoring in animals** and investigation of the distribution of SARS-CoV-2 in animal populations and whether there is a risk of the virus crossing back to humans again, resulting in a new pandemic	1	6%

* *Ranking ratio: Percentage of Advisory Forum members who selected this research gap as one of their three high-priority gaps*

Conclusions

Consultation with ECDC experts resulted in the identification of 22 high-level research gaps that were then organised into three thematic areas. The nationally nominated experts in the Advisory Forum assessed the list and confirmed that there were no obvious omissions. Notably, each of the 22 research gaps received support as a high priority area for further research from at least one Advisory Forum member during the ranking exercise.

The first thematic area addressed COVID-19 biology and the intersection with human host populations. This area has a strong basic research element, with knowledge gaps relating to improving understandings of natural infection, disease course and aspects inherent to the underlying biology of SARS-CoV-2. This basic knowledge base is foundational and is therefore important to inform and support targeted research that aims to address and inform public health action.

The five knowledge gaps in this thematic area were relatively broad, but there was a clear consensus in the Advisory Forum that research to improve understanding of 'immunity and immune response', and characterisation of the 'burden of disease' and overall clinical impact, were the two areas that warranted the highest priority for further research (prioritised by 95% and 80% of Advisory Forum members, respectively). Immune response is central to many aspects of COVID-19 outcomes, including host factors such as susceptibility, infection, pathology and disease severity. Understanding of mechanisms and duration of immunity in different population groups, including the role of natural or hybrid immunity in longer term protection, is also fundamental to inform current and future vaccination strategies. Enhancement of knowledge on the overall burden of COVID-19 to better understand the clinical spectrum and consequences of infection, including long-term manifestations (post COVID-19 syndrome and the long-term sequelae following infection and intensive care unit care) are also needed to inform future healthcare needs and public health responses to COVID-19.

The third priority knowledge gap in this thematic area was the need for research on the 'biological mechanisms of transmissibility and severity' (prioritised by 47% of Advisory Forum members), which illustrates that there is still much uncertainty about the fundamental biology of SARS-CoV-2 infection and COVID-19 disease, including the underlying basis of pathogenesis and the variance in clinical and epidemiological profiles between different strains. Further collection and analysis of 'contact pattern data', the next priority knowledge gap (40%), is key to

understanding and predicting drivers of infection. ECDC Modelling teams were particularly strong advocates for this, as contact patterns are a key parameter in modelling and forecasting work and such advances would improve the ability to track, predict and manage future outbreaks of COVID-19 (and other infectious diseases). Research directed at 'healthcare-associated SARS-CoV-2 infections' was supported as a key knowledge gap by five Advisory Forum members (33%). This was the most targeted research activity of the five presented within this thematic area, which may have contributed to it receiving lower levels of support than more high-level actions. The ECDC experts who identified this as a knowledge gap noted that the mechanisms of transmission and options for mitigation remained a neglected area of research, despite clear evidence of significant COVID-19 transmission and burden in healthcare settings such as long-term care facilities.

The second thematic area consolidated research actions to inform pandemic response. A clear majority (80%) of Advisory Forum members selected 'the systematic evaluation of prevention and control measures' as one of their three high-priority research gaps. In subsequent commentary, Advisory Forum members stressed that although non-pharmaceutical interventions (NPIs) remain at the forefront of public health mitigation approaches against COVID-19, the knowledge base remains limited on the effectiveness of individual measures or the relative effectiveness of each measure in combination. Improved understanding of the effectiveness of NPIs remains highly relevant for future mitigation, particularly in scenarios where protective immunity diminishes because of viral mutation or waning immunity. Advisory Forum members also emphasised methodological constraints in evaluating NPI effectiveness using observational study designs and suggested research be conducted to propose and evaluate alternative methodical approaches.

Two-thirds (67%) of Advisory Forum members also selected research to understand the public health (and economic) losses or setbacks related to 'other infectious and non-infectious diseases' during the COVID-19 pandemic. This reflects the need to obtain a deeper understanding of the broader health and societal impacts of COVID-19-related measures in order to inform proportionate mitigation approaches in future and possibly rebalance public health research and policy towards other priority areas. Approximately half (47%) of Advisory Forum members identified research into 'political, behavioural and social sciences' as a priority to deepen understandings of behavioural, cultural and societal drivers that facilitate or inhibit population acceptance/adherence to public health interventions. This included advancement of methodologies to further improve data collection and assessment of these dimensions.

Further work to inform vaccine formulation and develop effective 'new vaccines and therapeutics against SARS-CoV-2' was considered a high priority by four Advisory Forum members (27%). In relation to this point, an Advisory Forum member commented that industry should be central in (pre-licensing) pharmaceutical development. This may reflect an assumption that innovation research for novel vaccines and therapeutics is already well established and resourced, and therefore less deserving of specific focus. However, public health uncertainties persist regarding optimal use of approved vaccines, vaccine composition, and strategies to maintain vaccine uptake and protection in different populations groups and against a backdrop of vaccine hesitancy. The remaining knowledge gaps in this thematic area – such as the need for 'operational research into ventilation systems' (prioritised by 20% of Advisory Forum members), understanding the impact on and building resilience in the 'healthcare workforce' (prioritised by 7% of Advisory Forum members) and the need for more 'implementation science' (prioritised by 7% of Advisory Forum members) – may have received less support because they focused on discrete rather than broad-based research actions. The low ranking of research on 'vulnerable groups' provoked some discussion in the Advisory Forum, as only three Advisory Forum members (20%) selected this as a high priority despite the fact that the predominant pandemic burden has been carried by the medically and socially vulnerable, as well as by the healthcare systems that have responded to care needs from these groups.

The third thematic area encompassed pandemic (re-)emergence and new variants. There was a clear consensus that research into 'novel surveillance and monitoring strategies' was the highest priority (supported by 14 members; 88%) in this area. Research to 'optimise public health responses to prevent or mitigate a new pandemic', including enhancing capacity for rapid containment and control in the early phases of a potential COVID-19 pandemic (re)emergence, was selected as a high priority by 11 (69%) Advisory Forum members. Half (50%) of Advisory Forum members also identified research to 'characterise human host populations' to enable understanding of the epidemiological impact of underlying variance in global populations as a priority to aid interpretation of emerging infection risk. Five Advisory Forum members (31%) selected research to inform and optimise 'data access, integration and data-system approaches' as a high priority. This reflects the increasing importance of data linkage and opportunities to address policy-relevant questions through multi-domain analysis using combinations of clinical, epidemiological and genetic data sets. The remaining three research priorities in this area covered relatively diverse topics: systems biology approaches to inform drivers for 'pandemic emergence' (prioritised by 31% of Advisory Forum members), molecular-level research on 'genetic characterisation' to improve understandings of genetic evolution as a pathway to predict genotypic change and phenotypic outcome (prioritised by 19% of Advisory Forum members) and macro-level, surveillance-based approaches for real-time 'monitoring of animals' to support early identification of COVID-19 emergence (prioritised by 7% of Advisory Forum members).

Discussion

This ECDC expert consultation to identify current and future COVID-19 knowledge gaps illustrates that the knowledge base used to inform EU public health action against COVID-19 remains incomplete despite the significant global and EU research investment and resulting scientific knowledge that has been acquired since SARS-CoV-2 emerged in late 2019. This partially reflects the dynamic epidemiological situation around COVID-19, including the ongoing emergence of new variants against a backdrop of increasingly complex immunological profiles within EU/EEA populations. Therefore, research efforts must be continued to ensure policy actions are informed and underpinned by robust scientific evidence.

This exercise coincided with the third World Health Organisation (WHO) Global Forum on research and innovation to address COVID-19. The forum took place from 24 to 25 February 2022 (one day after the Advisory Forum performed the ranking exercise on the 22 knowledge gaps identified by ECDC experts), and brought together many leading experts to 'review and identify core thematic areas of research and highlight knowledge gaps and research priorities in the next research phase'. The aim and scope of the forum paralleled the work described here and the resulting report [7] summarising current global knowledge gaps and research priorities offers a useful comparison.

The WHO forum identified five high-level areas for future research gaps. The first and last focused on strengthening global research capability and long-term investment in pandemic preparedness and action, respectively. The remaining three areas focused on directed data and information generation to guide the COVID-19 response. Although these were sometimes targeted towards aspects that are somewhat outside of ECDC's scope (e.g. regulatory science, patient management, clinical care pathways and research on new therapeutics), many had public health aspects that align with the scope of this report and the research gaps identified by ECDC experts.

In general, there is concordance between the public health knowledge gaps identified by the WHO forum and the prioritised areas proposed by ECDC experts. There was a common recognition of the importance of ongoing research to understand epidemiological parameters such as drivers of transmission and severity to underpin the existing primary knowledge base. Research to better understand the natural history of SARS-CoV-2, as well as dynamic virus evolution and its impact on key epidemiological parameters and ability to detect and diagnose infection, were also prominent. Like the ECDC Advisory Forum, the WHO forum emphasised early detection of emerging pathogens as an ongoing priority and highlighted the importance of genomic sequencing capacity to monitor emergent variants, as well as research to improve abilities to predict and interpret genomic data. The importance of monitoring the human-animal interface was also identified, including targeted surveillance in animal populations and targeting hotspot species and locations of potential emergence. The WHO and ECDC assessments both identified research gaps to directly inform the pandemic response. Methodological challenges to assess the effectiveness of control measures were also highlighted. In relation to public health interventions, both ECDC and the WHO forum emphasised the importance of research to advance the optimal use of vaccines, including research to evaluate effectiveness within a complex epidemiological background of rapidly changing virus strains and fluctuating population immune status.

However, there were some differences in emphasis between the ECDC and WHO prioritisations, including (among others):

- greater priority was given in the ECDC rankings to the importance of research to manage and utilise large datasets and harness the power of 'big data' through multi-domain analysis, and the need for research to understand and mitigate the impacts of COVID-19 on other infectious and non-infectious diseases
- greater priority was given by the WHO forum to improve the knowledge base to support public trust in public health and social measures and the need for multidisciplinary research to gain a rounded evidence-base to inform future intervention approaches. The WHO forum also emphasised research to inform and manage the infodemic surrounding the COVID-19 pandemic, including research to measure and monitor the impact of the overabundance of information and to develop options to mitigate against harmful effects. The WHO forum also placed more focus on COVID-19 infection prevention and control in healthcare settings and protection of healthcare workers; while this was also identified by ECDC experts, it was not highly prioritised by the Advisory Forum.

A similar ECDC-led exercise that was undertaken in 2020 to identify policy-relevant knowledge gaps to support COVID-19 public health response identified many knowledge gaps that remain relevant now. For example, the need to 'quantify the contribution of different NPI and social measures on the trajectory of the pandemic', identified in 2020, remains a pertinent and outstanding need that should be prioritised in order to target future interventions. However, there is now a greater emphasis on sustainability of measures. The earlier exercise emphasised research to inform effectiveness and compliance of NPIs, as these were the only interventions available at that time, and the indirect and longer-term impacts were of less concern. There is now greater recognition that the evidence base needs to inform a balanced approach to interventions that maximises public health impact but minimises direct and indirect negative consequences.

Comparison of the research and knowledge gaps identified and prioritised in this exercise with those from the exercise in 2020 exemplifies both the progress of research and the changes in perceived uncertainties towards COVID-19. For example, research to understand the impact of seasonality, environment and climate was identified as a key research theme in 2020. This presumably reflected a concern that future influenza-like seasonal peaks could have exacerbated the COVID-19 burden prior to the first COVID-19 winter in the EU/EEA. These concerns were not identified as priority research gaps in this exercise, as knowledge has accumulated – to some degree – through the experience of two full years of the pandemic (although important uncertainties remain). In contrast, many of the surveillance actions identified in 2020 remain pertinent despite significant efforts to improve data systems and monitoring in the intervening years. The knowledge gaps identified in 2020 included prevalence of infection in different population groups, evolution of population seroprevalence and surveillance of severe infection. Despite enhanced and targeted surveillance approaches in the EU/EEA, such as dedicated research to support and coordinate COVID-19-specific longitudinal cohort studies [8]), these remain at least partially unfulfilled. For example, there remains uncertainty regarding the underlying prevalence, risk profile, clinical spectrum and biological mechanisms of long-term sequalae following SARS-CoV-2 infection. Limitations on abilities to consistently link biological data to 'real-world' clinical outcomes also hinder options to improve and target interventions, including virus neutralisation and protection from vaccines.

Looking back at the 2020 report demonstrates the evolution of COVID-19 knowledge and illustrates that there is a need to continuously evaluate the existing knowledge base and consider what research is required to address future public health action. Comparison of the current report with the results of the WHO Global Forum also demonstrates that although the knowledge and research gaps identified by global health actors are fundamental to inform EU responses, there may be some variance in the priorities for EU research. These differences reflect both the perspectives of EU/EEA scientists on which gaps are important, but also the COVID-19 policy landscape that determines the responses that are in place or that may be enacted in the future. Therefore, there is value in ECDC performing regular exercises to identify and prioritise COVID-19 knowledge and research gaps in order to obtain and share insights on current and future research needs in an EU/EEA context. More fundamentally, COVID-19-related research action and knowledge generation remain critical. There is still much to learn about COVID-19 and the public health approaches that may mitigate its impact. Ongoing uncertainties partially reflect the dynamic epidemiological situations around COVID-19, but this report demonstrates that there are knowledge gaps in several key areas and that research efforts must be continued to ensure policy actions are informed and underpinned by robust scientific evidence.

Limitations

A key limitation in the ranking exercise undertaken by the Advisory Forum was the limited opportunity for participants to give specific input on the rationales behind their choices. Further insight into Advisory Forum members' reasoning would have been helpful to understand the basis of selection. Nonetheless, the Advisory Forum were encouraged to consider public health benefit, feasibility and cost of each research gap in their prioritisation through the IRIS methodology, which provides some insight into how their selections were made.

The 22 research gaps were allocated into three discreet thematic areas, and ranking was conducted independently within each area, could not across different thematic areas. Hence knowledge gaps in different thematic areas could not be directly compared during the ranking exercise. In future, this could be achieved by conducting a single ranking exercise of all primary knowledge gaps identified.

Next steps

This report aims to support future thinking and actions towards research on COVID-19 and pandemic preparedness at national and EU levels in order to:

- assist in developing content for future research actions and calls targeting public health, preparedness and other areas relevant to ECDC and its stakeholders and
- leverage ECDC's expertise and the insights from EU/EEA representatives through proactive input into research cycle planning.

This consultation and subsequent ranking exercise served as a pilot for future disease-specific research assessments, as similar approaches could be used to gain insight into research gaps from experts at ECDC and within established disease-specific networks in the EU. Initial feedback from the Advisory Forum was generally positive towards the approach used in this exercise. It is also possible that the Advisory Forum could play a similar role in reviewing proposed research activities and performing prioritisation exercises to assist in guiding final actions.

ECDC will undertake an internal assessment of the methods and outcomes of this project to support improvement and refinement of the approach. Input from stakeholders to inform future actions is welcome.

Contributing ECDC experts (in alphabetical order)

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References

1. Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European Centre for Disease Prevention and Control, (2004).
2. European Centre for Disease Prevention and Control (ECDC). ECDC Strategy 2021–2027. Solna, Sweden: ECDC; 2021. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/ECDC-Strategy-2021-2027.pdf
3. European Commission. Coronavirus research and innovation: "EU supported research and innovation projects and initiatives to tackle the spread of coronavirus and preparedness for other outbreaks". European Commission; 2021. Available at: https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation/coronavirus-research-and-innovation_en
4. Organisation for Economic Co-operation and Development (OECD). Mobilising public research funding and infrastructures in times of crisis 2021. Available at: https://www.oecd-ilibrary.org/content/component/e96ef24b-en
5. Semenza JC, Adlhoch C, Baka A, Broberg E, Cenciarelli O, De Angelis S, et al. COVID-19 research priorities for non-pharmaceutical public health and social measures. Epidemiol Infect. 2021 Apr 5;149:e87. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33818348
6. de Carvalho Gomes H JA, Kramarz P, Giesecke J. IRIS—a tool for prioritising guidance development at the European Centre for Disease Prevention and Control (ECDC). 2013. Available at: https://abstracts.cochrane.org/search/site?f%5B0%5D=field_year%3A24
7. World Health Organization (WHO) WHO. How global research can end this pandemic and tackle future ones Building a resilient research architecture and capability to protect us all 2022. Available at: https://www.who.int/publications/m/item/how-global-research-can-end-this-pandemic-and-tackle-future-ones
8. European Commission. Outcome of HERA Incubator call for expressions of interest on coronavirus variants: 11 projects European Commission; 2021. Available at: https://ec.europa.eu/info/files/outcome-hera-incubator-call-eoi-coronavirus-variants-11-projects_en

Annex 1. Summary of the main points raised during consultations with ECDC experts, by scientific group, February 2022

Scientific Group	Knowledge and research gaps identified
Infection Prevention and Control (IPC) group	Very basic research into characterising SARS-CoV-2, with a focus on understanding the biological mechanisms behind transmissibility and in particular the relative contribution of various routes of transmission. Also, research into the where, when, who and how transmission occurs in the real world, outside of experimental settings. Such settings include i) community indoor and outdoor settings and ii) healthcare in general wards and in specialised settings (such as intensive care or when 'aerosol generating procedures' are performed).
	Investigating the effectiveness of the various IPC measures, including the various elements of personal protective equipment that were deployed (or could have been deployed) during this crisis. If possible, aiming to quantify this and establish a relative scale in terms of effectiveness in meeting various public health goals.
	Research into appropriate ventilation systems in enclosed public places, covering the different types of ventilation and air filtering/cleaning available, how and where to place them to achieve the highest reductions in transmission, and the cost-effectiveness of the various options.
	Research into what the best methods are, in terms of reliability of data and feasibility, to investigate the effectiveness of public health/IPC interventions both in a pandemic crisis setting and outside of one.
	Research to identify optimal ways to apply knowledge when developing and implementing policies (from implementation science and evidence to decision frameworks)
	Analysing the performance of healthcare systems in terms of quality of care (healthcare-associated infections, attributable mortality – expressed both in absolute numbers and as burden of disease in standardised metrics (such as disability-adjusted life years (DALYs)) – to allow for comparison to other diseases, for easy comprehension and prioritisation) and exploring possible structural changes that could help reduce the burden of COVID-19.
Emergency Preparedness and Response Support (EPRS) group	Research into non-technical areas surrounding pandemic preparedness and response, including operational research, health/pandemic governance research, implementation science and social science. There is a large gap due to underfunding of these studies, combined with the fact that questions in these areas are often more challenging to research and answer with currently available methodologies. However, gaining an understanding of the societal response is vital for understanding and designing effective response strategies in the future, and should therefore be made a research priority going forward.
	Projects on the links between infections and chronic disease (also important for understanding the burden spectrum of infectious diseases in general and COVID-19 in particular).
	Research into non-pharmaceutical interventions (especially their social impact) and vulnerable groups, as well as the link between health and education.
	More research into zoonotic reservoirs.
	Reassessment of global lab safety standards, the dual-use dilemma in life sciences, etc. (research into the origin of the COVID-19 pandemic and laying the groundwork for understanding any emerging pandemics).
Microbiology group	Researching what the risks/opportunities/costs are of not adequately supporting our global or European data systems, looking specifically at data sharing between countries or different sectors within countries, generating timely data, and clinical and epidemiological data not being easily linkable.
	Exploring waste water monitoring systems to act as a complement to other surveillance activities (e.g. for the detection of new variants at specific settings: screening of waste water of aircrafts, at airports, at ports). Research into bioinformatics approaches to detect variants available in very low concentrations/volumes, to monitor infection status and trends in populations/the community and for an early warning system capable of detecting emerging variants.

Scientific Group	Knowledge and research gaps identified
	Monitoring in animals, both domesticated and wild, to explore whether the current extremely widespread distribution of SARS-CoV-2 in humans has translated to the virus transferring to certain animal populations as well, and whether there is a risk of the virus crossing back to humans again at some point resulting in a new pandemic.
	Research into drivers of virus evolution.
	Research into better methods to predict antigenic drift (i.e. escape from antibodies from vaccines or natural infection), viral transmissibility and severity of new variants based on genetic characterisation. Would be vital to allow for rapid predictions surrounding new variants and to allow for more informed decision-making.
	Basic research into characterising SARS-CoV-2, with a focus on understanding the biological mechanisms behind transmissibility and severity. Also research into the where, when or how transmission occurs – and in who – in the real world, outside of experimental settings.
Surveillance group	Research into testing strategies appropriate for reaching certain goals (e.g. reducing transmission or keeping hospitalisation levels manageable), looking at the effectiveness of the various strategies in reaching these goals, their cost-effectiveness and their acceptability from a societal perspective (effects on equity: cost, disincentives for testing in certain groups, etc.).
	Research into methods to rapidly characterise host populations and predict the severity of new strains in host populations with different characteristics, based on data from the primary location(s) where the variant first emerges. Could consider: age and general health status of the population, size and other characteristics of previous COVID-19 waves, past exposure to other pathogens, immunity levels, healthcare, geography, etc.
Modelling team	Studies on monitoring immunity levels, both natural and vaccine-acquired immunity, and studies especially looking at the changes in immunity levels in the population over time (rate of waning, etc.) are vital to inform modelling to predict the observed severity and transmission characteristics of new waves/variants.
	Characterising the burden spectrum of COVID-19, looking to move beyond only looking at hospitalisations and mortality, to get a more holistic view of the negative impacts of COVID-19, including post COVID-19 condition (including calculating disability-adjusted life years (DALYs)). This would allow for reframing of policy discussions and maybe change some intervention policies that on balance don't impact mortality as much as they may impact morbidity.
	Good, representative social contact pattern data. Currently, mobility is used as a proxy for this variable, but ideally for modelling COVID-19 we would like to be able to measure or estimate the amount and type of physical contacts that people are having (ideally including all of the following: hourly breakdown of the heterogeneity of contacts, stratified by age, intergenerational contact or not, vaccination status, etc.).
Behaviour team	Of the many policies and interventions implemented during the course of this pandemic, very few are getting systematically evaluated for effectiveness or their impact from a behavioural and social perspective (acceptance, impact of health outcomes, unintended consequences). This is partly because of the methodological challenges inherent in evaluating complex public health interventions from a behavioural science perspective. Current 'gold-standard' methods are either unable to capture these complexities (for example, use of randomised controlled trials to determine acceptance of non-pharmaceutical intervention policies or vaccine uptake strategies) or may be considered too time-consuming and resource intensive to run from a government/decision maker perspective (for example, realist evaluations). There is therefore a strong need for research into methodological development for more robust evaluations. This would also allow decision makers and governments to understand what measures may be more effective should they need to re-deploy similar strategies/interventions in the future.
COVID-19 and influenza, and Scientific advice group	Cross-cutting topics: COVID-19 transmission biology; determining correlate(s) of protective immunity for different outcomes (infection, severe disease, death); understanding the duration of protective immunity and waning over time (see Modelling); evidence-based global standardisation of variant threat evaluation to facilitate high throughput risk evaluation and public health action based on diagnostic capability, immune escape potential (susceptible human population), human-to-human transmission potential and disease severity; animal population (reservoir) screening (see Microbiology); effectiveness of public health measures; and air ventilation (see IPC).

Scientific Group	Knowledge and research gaps identified
	Could a different response at the beginning of the pandemic have prevented the pandemic from taking off and what would be needed/what would we need to do to prevent the next pathogen with the potential to cause a pandemic from reaching that stage? Is there a tipping point or threshold above which a pandemic becomes unavoidable and can only be delayed? Response strategy, human resources, contact tracing and understanding the breaking of contact chains are all areas amenable to research for answering these questions.
	Regular age-specific seroprevalence monitoring systems using leftover serum for estimating the burden of disease at international, regional, national and subnational levels. Should not just be put in place for COVID-19, but extremely useful for monitoring a whole panel of diseases. Useful complement to other monitoring systems (see Microbiology).
	Research into the impact these two years of serving on the frontlines has had on the healthcare workforce. Questions around burnout, best methods of rehabilitation and how we can better equip our healthcare workforce to deal with stressors (also in the event of future pandemics).
Vaccine-preventable infections team	Vaccine formulation and development of new vaccines.
	Vaccine behaviours (including acceptance and drivers for uptake).
	Immunity: duration and magnitude (stratified by age/target groups, number of vaccine doses (e.g. third or fourth dose against a specific variant), previous infection and vaccination status).
	Vaccine effectiveness against post COVID-19 condition (long COVID), severity of disease and protection against transmission.
	More research into alternative study designs and methods because the questions we have are hard to answer with currently available methods. Including a review of GDPR and how these practices have changed research and timeliness.