Attitudes and Expectations of Investigations and Evidence for Biological Attribution

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Biological events—including outbreaks and pandemics, biological weapons use, or accidental laboratory release—have the potential to be extremely disruptive. The ability to accurately investigate, identify origins of, and attribute these events is critical for deterring deliberate events and implementing interventions to prevent future natural or accidental events. However, historical examples of biological event attribution and origins investigations illustrate significant gaps in processes, from technical capabilities to communications, and have lacked conclusive consensus among decision makers, the public, and scientists. This study aimed to assess attitudes and expectations of a broad range of stakeholders regarding investigations and evidence generated for biological attribution. We interviewed 41 experts in disciplines related to attribution and investigations and analyzed interview content using a mixed-methods approach. Interviews generated a list of factors to consider when planning or conducting investigations, presented here. Opinions concerning the conduct and reporting of biological samples analyses and perceptions of feasibility of attribution varied among interviewees representing different fields of study. Participant opinions varied less in regard to requirements, protocols, and guidelines thought to be important to maintain confidence and trust in an investigation and evidence. Findings from this study can inform planning for future events.

Keywords: attribution; microbial forensics; Biological and Toxins Weapons Convention; nonproliferation policy; weapons of mass destruction; origins; investigation; biosecurity

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Introduction

Biological events such as outbreaks, pandemics, and biological attacks can have dire consequences for human and animal health, economics, and security. The COVID-19 pandemic clearly illustrates the disruption biological events can have on all aspects of life. The pandemic also demonstrates a prime example of the importance of understanding the cause of a biological event. Debate over the origins of the COVID-19 pandemic has raged since January 2020, when conspiracy theorists first alleged the virus was created for economic reasons. Since then, there have been accusations that SARS-CoV-2 was created to be a bioweapon and suggestions the virus was accidentally released from a laboratory. The World Health Organization (WHO)[i] and many leading experts in viral evolution[ii] have maintained that the virus is naturally occurring. The confusion and debate over origins has enabled exploitation of the situation for political ends and been used to justify xenophobia while detracting from resources that could have been used to respond to the event or prevent future pandemics from occurring. While this work does not explore the origins of COVID-19, this debate illustrates why there must be robust tools and frameworks in place for investigating biological event origins.

Attribution is a key component to understanding the origin of a biological event. Attribution typically refers to assessing the source of a given event or agent. In the weapons of mass destruction (WMD) field, the ability to successfully attribute an attack is considered a deterrent for future attacks.[iii] Investigations for attribution typically rely on several types of evidence, including intelligence signals and scientific evidence.[iv] Investigations and tools for determining the origin of chemical spills in the environment or chemical attacks have aided in responding to events[v], developing interventions to prevent a similar event reoccurring[vi], and holding responsible parties accountable.[vii] The Organisation for the Prohibition of Chemical Weapons (OPCW) is an international authority responsible for implementing the Chemical Weapons Convention (CWC), the arms treaty banning the use and development of chemical weapons.[viii] The OPCW investigates chemical weapon development and use and continuously engages in research and development of tools for chemical attribution. The biological counterpart to the CWC, the Biological and Toxins Weapons Convention (BWC), has no equivalent organization to the OPCW to focus on biological risks.[ix] There is a mechanism by which the United Nations (UN) Secretary-General may investigate an alleged use of a

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chemical or biological weapon by any country, known as the UN Secretary-General's Mechanism (UNSGM), but this scheme has never been used for a biological event. While there are examples of investigations into deliberate biological events, such as the Amerithrax investigation[x] and Rajneeshee cult investigation[xi], these have been limited to the jurisdiction of a single country rather than requiring international cooperation. Furthermore, many of the historical examples of biological event investigations took place before critical advancements in the life sciences, such as high throughput DNA sequencing, and are therefore not adequate models for the investigations that would occur today. Without a biological equivalent to OPCW and more modern case studies, attribution for biological agents has not been well studied and there is no clear implementation mechanism for an investigation into the origins of an accidental or deliberate biological event, creating a dire gap in our ability to prevent a biological event with severe health, economic, and societal consequences.

This study sought to understand the various expectations and attitudes of relevant stakeholders toward investigations and evidence for attribution of biological events. We interviewed stakeholders from a wide range of disciplines concerning their thoughts on evidence for attribution. This article presents responses from participants for both the evidence itself and the processes surrounding its collection, analysis, and interpretation.

Methods

Between February and May 2022, 41 semi-structured interviews were conducted virtually with key informants representing a wide variety of expertise relevant to biological attribution. Areas of expertise represented include microbial forensics, molecular biology, microbiology, bioinformatics, genetic engineering, virology, bacteriology, biochemistry, public health, epidemiology, international security, non-proliferation, international relations, intelligence, law, biosafety, and biosecurity. Perspective interviewees were identified based on an informal literature review and by employing snowball sampling. The interviews explored participants' opinions concerning the types and characteristics of evidence potentially collected for attribution, processes possibly utilized in an investigation, feasibility of attribution, and perceived barriers and facilitators to attribution. All interviews were conducted on a not-for-attribution basis due to the potentially sensitive nature of the topic and audio recorded following participant consent.

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Recordings of the interview were transcribed and analyzed using a mixed-methods approach. Transcriptions of the interviews were qualitatively coded using NVivo qualitative coding software (Release 1.6.2) by an individual coder. The initial thematic coding framework was developed after the tenth interview was completed and added to as new themes emerged in subsequent interviews. The final thematic coding framework was used to code all interviews following the last interview and included categories such as investigatory steps, evidence, barriers and facilitators, and roles.

Following coding, a quantitative analysis was conducted to identify priority topics. NVivo and Microsoft Excel were used to generate quantitative metrics for all the codes in the framework to assess how frequently the topic was mentioned. Codes or co-coded pairs present in at least 10 interviews were considered priority themes for the final targeted thematic analysis. The targeted thematic analysis was conducted on the coded text corresponding to the priority themes.

This work was conducted under the purview of the Johns Hopkins University Bloomberg School of Public Health Institutional Review Board as human subjects research (IRB 00018728).

Findings

Interviews and Quantitative Analysis

A total of 41 interviews were conducted, one of which included two interviewees. Participants represented 12 countries covering 6 continents. Thematic coding was performed on 41 interview transcripts resulting in 3,753 total coding references and 8,049 co-coded references. Of the 146 codes in the final coding framework, 102 were addressed in at least 10 interviews and there were 88 co-coded pairs.

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Defining Attribution

Participants were asked to describe what "attribution" for a biological event entailed. There was a broad range of answers; some participants considered attribution to include both determining the type of event (naturally occurring, accidental, or deliberate) and who, if anyone, was responsible for the event, while others considered only the latter question to be attribution. Multiple participants noted that determining the responsible party is highly complicated. Responsibility may lie with the person who physically released an agent, the people who created or manipulated the agent that was released, and the people who funded the work. Furthermore, other actors may have indirectly enabled a biological event, which may be enough for some to find them responsible. The process for determining responsibility across these different roles will be different. Investigators will need to ask different questions and gather different types of evidence to effectively assess the full line of individuals responsible for a biological event, just as is true for other types of investigations.

Expectations during Different Stages of Investigations

The methodologies and protocols used in an investigation and evidence collection were discussed with participants. While some aspects of an investigation were nearly universally mentioned by participants as critical, other areas had more divergent opinions. Considerations for attribution shared by participants were organized into groups by stage of the investigation and theme. Table 1 includes some these considerations organized by stage and factor.

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	Stage of Investigation			
Factor	Initiation	Gathering Evidence	Analyzing Evidence	Reporting
Accessibility	• Host country blocking entry • War zones	• Access to evidence • Access to site(s) • Safety of witnesses and investigators	• Accessibility and familiarity of technologies used for analysis	• All countries have access to same information • Publicly available information
Timeliness	• Political willpower • Public interest	•Sample viability	• Sample viability	• Accountability • Interventions
Trust	• Scientist, not politician, leading investigation • Potentially no people with P5 nationality	• Standardized methods for collection • Onsite vs remote collection • Chain of custody	• Validated methodologies • Triplicate analysis • Ownership of data • Including uncertainty measurements	• Include controls and validations • Just the facts, no opinions • Accurately reflect disagreements • Privacy vs transparency
Coordination	• Creating investigatory team • Coordinating with country of interest • Travel to site	• Logistics of travel	• Between investigators and laboratories • Between agencies involved • Between members of investigatory team	• One designated spokesperson • One agency/team briefing
Cooperation	• Between nation and investigators	• Ownership of samples • Access to all necessary sites	• Between investigators and laboratories • Settling disagreements between investigators • Ownership of data	• All countries get access to same data/information
Neutrality	• Geographically diverse • Appropriate expertise on investigatory team	• No cherry picking what evidence is collected	• Known, trusted laboratories not associated with a government	• No information leaks
Perception	• Diversity of investigatory team • Appropriate justification	• Types of evidence collected • Chain of custody	• Validated methodologies • Rigorous science and review	• Politically motivated attacks will happen, have strategy to respond
Flexibility	• Negotiating investigatory team membership	• Different types of evidence	• Using less than state-of-the-art methods	• Responding to mis-/disinformation
Procedures	• Appropriate authority initiates • Allowable scope	• Standardized methods for collection and chain of custody	• Preapproved methodologies • Laboratories only doing what is allowed by investigation lead	• Trained spokesperson appointed and all communications filtered through them
Politics	• Selection of mechanism to initiate investigation	• Regardless of politics, all theories investigated	• Ensuring analysis is beyond reproach to minimize options for politically motivated attacks	• Attacks on validity • Choosing next steps

Table 1. Matrix of Factors Impacting Attribution and Investigations of Biological Events Identified by Participants.

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Mechanisms for Initiating Investigations

A key challenge most of the policy-oriented participants mentioned regarded how to initiate an investigation. In general, participants felt an investigation would be more plausible at the national level than international level. At the national level, law enforcement would lead the investigation in many countries. Some nations have members of law enforcement with specialized knowledge in biological events as well as mechanisms to bring in government experts who may have additional specialized knowledge. However, many countries have never had to investigate biological events, which may pose a challenge to investigating in an emergency.

On the international level, there are limited options for initiating an investigation. One option is the UNSGM, which requires a nation to formally request the Secretary-General initiate an investigation into a potential chemical or biological weapons event; however, this mechanism has never been used for a biological investigation (only chemical to date). Two benefits of the UNSGM pathway are that the Secretary-General has sole discretion to decide if an investigation will be initiated, rather than needing consensus from the UN Security Council (UNSC), and there are established guidelines for how to conduct UNSGM investigations.[xii] However, some participants expressed doubt concerning how prepared the individuals on the UNSGM roster would be if called upon to join an investigation. The list currently has 530 qualified experts but is not publicly available.[xiii] Some participants were concerned that those on the roster may be too senior and may not work in the laboratory or field on a day-to-day basis, making them less effective or prepared to be investigators.

Another option for investigation of biological events at the international level is Article VI of the BWC, which allows a state to request that the UNSC investigate alleged breaches of the BWC.[xiv] Participants were wary of this option because it has not been used in the past and is thus untested and challenged. Additionally, this pathway relies on the UNSC, which means an investigation could be blocked by one of the permanent members. Unlike the CWC, which created the OPCW, the BWC does not have an organization dedicated to the implementation of the treaty that could employ experts to support an investigation.

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Some participants, all of which were scientists by training, suggested the WHO take on the role of investigating biological events, but others (primarily those with expertise in public health or international policy) strongly felt the body should not be tasked with such a responsibility. The WHO currently has the mandate to respond to public health events and has investigated origins of outbreaks in the past to implement public health measures to prevent further events. However, it is not within the WHO mandate to investigate known deliberate events, and some participants worried that if the WHO were to begin investigating deliberate events, it could undermine the credibility and neutrality the body needs to achieve its public health mission. Another issue raised was that if a public health event (like an outbreak) is ambiguous at the beginning, the WHO likely will be the entity coordinating the response. As soon as evidence arises suggesting the event is not natural, however, the WHO no longer has jurisdiction to investigate the event's origin. Further clarity is needed regarding who determines the evidence is sufficient for the investigation to fall outside of the WHO's mandate as well who would then have jurisdiction. Current evidence overwhelmingly suggests the COVID-19 pandemic is a naturally occurring event.[xv] However, challenges arose with initiating an investigation, with the WHO needing to negotiate with the Chinese government to gain permission for a WHO-supported team to study the virus's origin in China; notably, the WHO was not allowed to call the study an investigation.

When participants were asked who could investigate a deliberate event on the international stage, they responded with contradictory answers. Two participants stated that an initiation of Article VI of the BWC would be equivalent to the UN Secretary-General activating the UNSGM. Others stated that an Article VI investigation could coincide with but remain separate from an UNSGM investigation. The United States, United Kingdom, and Canada previously presented this view in a working paper at BWC meetings.[xvi] Several participants also expressed doubt that Article VI would be a viable option because there are not clear guidelines or mechanisms to operationalize this pathway. Only two participants suggested the WHO could investigate a deliberate event. Most participants stated the WHO should not or could not investigate such an event, though many stated that the WHO would still be responsible for coordinating a public health response to a deliberate biological event.

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Forming Investigatory Teams and Defining Mission

All participants spoke about the importance of the investigatory team comprising individuals with diverse expertise and diverse geographic origins. For investigations being conducted by or on the authority of an international agency, 36 participants felt geographic diversity was deemed crucial for the investigation team to avoid undue scrutiny. If a team was composed entirely of people from one continent or one allied group, the integrity of the team would be questioned internationally. Five participants felt that citizens of countries that are permanent members of the UNSC should be entirely excluded from the investigatory team to decrease perceived conflicts of interest or avoid rejection of the investigation results based on the composition of the investigatory team.

In addition to geographic diversity, 31 participants encouraged the inclusion of diverse types of expertise on any investigatory team to provide further credibility. Common areas of expertise or experience included microbiology subspecialities (the sub-specialty needed changing based on the event), epidemiology, pathology, medicine, bioinformatics, biostatics, international law, biosafety, biosecurity, environmental health, social science, law enforcement, and public relations/communications. Participants also listed other areas of expertise that may be appropriate to include depending on the situation, such as experts in a particular geopolitical region or scientific subdiscipline. Participants emphasized that the investigatory team should be composed of people with subject matter expertise rather than politicians or entirely of law enforcement. Three participants noted that it may be beneficial to ensure at least some members of the investigatory team actively work in the field doing sample collection, even if they are not considered to be senior experts in their discipline, due to the importance of sample collection during investigations.

Participants were asked to describe who they thought should be the head of an investigatory team. Respondents were split on whether they thought the head of the investigation should be a well-respected scientist with technical knowledge or someone with a career in international relations who is well seasoned in dealing with international politics. Notably, there was consensus that the head of investigation must be considered a neutral party and widely respected in the international community.

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Many participants also stated that the head of investigation should be well-equipped to effectively communicate with the public, politicians and policymakers, and scientists.

Laboratories Involved in Investigation. Because there is no single international agency responsible for investigating biological events, especially those that may be accidental or deliberate, there is not one laboratory that is predesignated to handle analysis of samples collected in such an investigation. Instead, laboratories whose primary purpose is something other than analyzing samples for an investigation will need to be used to assess samples the investigatory team collects. Participants were asked to describe how they thought relationships between an investigatory team and laboratories should be handled. Most participants said the investigatory team should not be expected to conduct the analysis themselves in a new laboratory established for that sole purpose, nor should they be analyzing collected samples in their own home laboratories. Instead, laboratories that have been pre-screened, such as those on the UNSGM roster, should be used to analyze collected samples. Participants diverged, however, as to the level of autonomy the laboratories should have in conducting their analysis. Seven participants, many of which were practicing scientists, felt laboratories should have leeway to conduct the tests they feel most appropriate using methods they feel are most appropriate. The logic behind this being that the laboratories would be well-respected institutions and recognized leaders in their fields and, as such, would know best what should be done with samples. Conversely, 26 participants felt strongly that laboratories only conduct tests using only the methodologies ordered by the investigatory team to maintain order and ensure samples are not wasted. Three of the participants who stated the laboratory should only do ordered tests were scientists who said that by only doing analyses directed by the investigatory team, they would be under less scrutiny. Some participants fell somewhere in between these extremes and thought balance could be reached between ensuring the conduct of necessary tests while also allowing labs discretion to conduct additional testing.

According to the UNSGM protocols for investigations, at least three laboratories should be chosen to assess samples for any investigation, with two labs running tests as directed by the investigatory team and a third lab receiving but not testing the samples unless directed by the investigatory team in the case the first two labs find disagreement in their results.[xvii] Participants were asked if they thought the selected labs should be

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allowed to communicate with one another, and again participants were split, although more evenly than when asked about autonomy of the labs. About half of participants felt the labs should be allowed to communicate to optimize protocols and share information while others felt there should be total separation of the laboratories to maintain independence in results.

Investigation Scope. Many participants, especially those with experience working in international agencies, said determining an investigation's scope and ensuring it falls within the authority of the ordering entity were vital factors. Several participants felt that any investigation would be subject to politically motivated criticisms, such as the 2013 UNSGM Syria Chemical Weapons investigation (described below in more detail)[xviii] or the investigation into the 2018 Salisbury Novichuk poisonings[xix]. By clearly defining the scope of an investigation and ensuring that the investigative body has the authority to investigate at the level of the stated scope, participants stated there was a lower chance that a country could ignore or refute the investigation based on procedural grounds. One of the most frequently identified barriers to investigations and attribution was politically motivated actions to undermine, discredit, or sabotage the activity. Participants frequently emphasized the need to minimize opportunities for politically motivated attacks, especially related to the perceived integrity of the investigation or its results.

Participants often pointed to the 2013 Syria UNSGM investigation as a good example of the importance of defining scope and ensuring investigations stay within those bounds. In the 2013 Syria investigation, the mission team was instructed to investigate potential chemical weapons use but not to assess attribution due to political sensitivities. Participants familiar with the specifics of the Syria investigation described how difficult it was to stay within the prescribed scope given how information about use of a chemical weapon could also inform attribution. One example given illustrates the difficulty in separating these two topics concerned looking at the chemical's delivery method. The team determined that rockets were used to deliver sarin, which is important for illustrating a chemical weapon was used as it speaks to intent. However, in doing a thorough investigation of the rockets, the team also conducted a trajectory analysis, which points towards attribution. Some trajectory information was included in the final report of the mission team, though participants familiar with the matter stated there was

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much deliberation and consternation among leadership and foreign diplomats concerning the topic.

Evidence Gathering and Handling

Participants reported evidence gathering to be a critical point in investigations and one that is particularly complex for biological events compared to others. Taking samples in triplicate is the standard in the UNSGM protocol, but the definition of a replicate is not as straightforward for investigating a biological event. For example, if trying to assess the microbial population composition on a surface, you could use three swabs side by side to get three different samples. However, each swab would be sampling three different areas and it could be entirely possible that the agent of interest is only present where one of the swabs swiped, leading to disagreement among the results. Alternatively, a single swab could be used and then cut into 3 pieces or eluted and split into 3 aliquots, but with either of those options, there is a risk of contamination or of losing data if there is only a low level of an agent of concern. Thirty-two participants noted there needs to be more guidance and discussion on best practices for evidence gathering, especially related to environmental sampling.

A near universal comment from participants was the importance of maintaining evidence integrity, particularly through a strong chain of custody from collection to destruction or storage. Participants consistently emphasized the importance of ensuring evidence integrity, with many suggesting all steps that could contribute to maintaining evidence integrity, such as filming the life cycle of the evidence or using barcodes to electronically geolocate and track samples, should be pursued. Participants often said that despite the relative lack of guidelines for biological attribution investigations, especially considering the technology used for such an investigation is continuously advancing, using established standards for how to handle evidence and investigations is important. The International Criminal Police Organization (Interpol), United States Federal Bureau of Investigation (FBI), and UNSGM protocols were often cited as standards that should be used for investigations even if conducted outside the respective organizations' jurisdiction.

The source of evidence was also widely stated as something contributing to evidence quality and integrity. Samples collected by the investigatory team were commonly said

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to be the most trustworthy. Most participants considered samples collected by a nongovernmental organization less trustworthy than those collected by national authorities. This presents interesting challenges for biological event investigations. In many cases, the first sign that something is amiss is disease presentation in a healthcare provider. The initial samples for the event may be the most informative for determining who is responsible but are also the least likely to be collected by the investigatory team. Samples collected by medical practitioners or public health officials are collected using protocols set up with the aims of those organizations in mind, rather than law enforcement or investigatory goals. Chain of custody likely would not be as stringent as the standard used for law enforcement. Additionally, samples taken for public health purposes may be anonymized to decrease the risk of privacy invasion, but this is antithetical to what is helpful for an investigation. Any investigatory team will have to reconcile their need for certain samples with the limitations of the sample source.

Types of Evidence. Participants were asked to describe the types of evidence they expected to see during an investigation into the origins of a biological event. For many participants, there was a list of evidence they wanted to see for any type of event, regardless of the type. Commonly listed evidence broadly falls into 3 categories: biological samples, witness accounts, and documentary evidence. Evidence types mentioned by participants can be found in Table 2.

Types of Evidence Mentioned
Epidemiological Data
Medical Records
Eyewitness Statements
Victim Statements
Whistle blower
Transcriptomic Analysis
Genetic Analysis of Victim
Fingerprints
Surveillance Video

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Isotopic Analysis
Histopathology
Prox Card Access
Cell Phone/Wearable Tech Tracking
Cell Phone History
Search History
Financial Data
Intelligence Signals
Laboratory Order History
Environmental Sample Analysis
Genetic Analysis of Agent
Weather Records

Table 2. Types of Evidence Named by Participants as Important.

Event Specific Considerations. When asked about how the type of event could impact the evidence of the investigation, participants offered a wide range of responses. Many noted that the type of event may be ambiguous, especially at the onset, but as evidence is collected, the type of event may become clearer, though perfect certainty may not ever be possible. Ambiguity in event type can hinder investigations, as jurisdiction would change depending on event type. Naturally occurring events often fall under the jurisdiction of public health authorities, such as the WHO. Once an event is not considered natural, public health authorities may be unable or unwilling to be responsible for investigating the event as such examination may be outside their mandates and/or capabilities. Participants noted that it is unclear who is responsible for investigating an event that is not naturally occurring, or even making the determination

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an event potentially is not natural, at the international level. Such unclarity may provide individuals or states an opening to spread mis- or disinformation for their own gain, which some participants warned could lead to greater biological threats in the future.

Within the deliberate event category, participants noted there are 3 main types of events—assassination, war, and terrorism—with each of these event types having different associated challenges. For example, access to the site could be exceptionally challenging in a war or conflict zone. With terrorism or a war zone, an event may be claimed or unclaimed. If the event is unclaimed, then officials may be unaware something has happened until a person or animal seeks medical care, at which point vital evidence may be lost. In an assassination, local law enforcement likely will be the first on scene and to collect evidence, which may be a point of scrutiny (e.g., suggestions of cover ups) if an international investigation is initiated later.

Within the accidental event category, participants mentioned two main types of events—accidental laboratory escape or a stockpiling or production accident. Sixteen participants felt that determining if an event was accidental would be easier than determining if the event was deliberate because an accidental event should have facilities with more evidence for a positive comparison. One participant felt the opposite would be true; with an accidental event, there may be significant interest in trying to cover up the event, which could drive people or institutions to destroy evidence before investigators can collect it.

Some participants suggested that all types of biological events should be considered and investigated, regardless of the initial evidence. This way, potentially relevant evidence for any scenario would be collected through the rigorous methods used by the initial investigatory team, reducing the chance of samples pointing toward one scenario over another and avoiding the introduction of bias in analyses. Additionally, some participants thought by starting any investigation with the understanding that the event could be natural, accidental, or deliberate, investigators would be more open minded and more likely to find “the truth.” Some stated that regardless of the suspected type of event, investigators must assess the breadth of ramifications of the biological event because its implications could point to potential motives if it were a deliberate event. Participants were very clear, however, that assessing an event’s impacts and potential

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motivations should be used to develop hypotheses that direct further investigation but never outweigh physical evidence pointing toward a different conclusion.

Access to Evidence. Many participants stated that access to information is one of the key barriers to a successful investigation. Again, using the 2013 Syria example, several participants pointed out the challenges of collecting information and samples when there is limited access to a site. In the 2013 Syria investigation, the investigatory team had only a few hours to access the site safely and collect as many samples as they could because the rebel groups controlling the area allowed them entry for only a short amount of time. Sixteen participants discussed potential evidence that can be collected remotely, but fourteen of those participants felt that onsite evidence was stronger than remote evidence. Another consideration mentioned for investigations in conflict zones was the ability to safely interview witnesses when the group controlling the area is closely monitoring the investigators and people with whom they speak.

Participants said timing is another critical element impacting access to evidence. Several noted how quickly evidence could be degraded or otherwise lost, especially the initial biological samples that many felt are vital for determining origin. Many participants cited moving an investigatory team onsite as quickly as possible as a priority to increase the chance of being able to collect the most useful samples.

Evidence Assessment and Interpretation

Once a sample is collected, the investigatory team needs to conduct analysis and interpret results. This investigatory stage—known as evidence assessment and interpretation—elicited the most diversity in opinion from participants. Nearly all reported this stage to have a variety of significant potential pitfalls, but there were significant contradictory opinions about the details of how evidence assessment and interpretation should be conducted.

In the life sciences, even slight variations in protocols can lead to drastically different results for some methodologies.[xx] There are also often several slight modifications that could be made to a protocol, any of which can produce a slightly different result. For example, there are hundreds of protocols to sequence one pathogen. While this is helpful for generating data for scientific exploration, it is a challenge for an

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investigation. Just as participants cited chain of custody as critical for evidence integrity, many said having validated and trusted methodologies is similarly vital for integrity. Most participants felt that an investigation should stick to methods that are well known and widely used, as these are methods that are more easily assessed by the broader scientific community, easier to validate, and more familiar to the broader scientific community. Using tools and methods that are more understandable and accessible may increase the willingness of policymakers to accept results and decrease opportunities for critics to attack an investigation. Alternatively, some participants said using cutting-edge methods may improve an investigation because they could provide highly relevant information that more traditional methods cannot.

To increase trust and validity, both scientific and perceived, many participants remarked that having guidelines on the conduct of evidence assessment and interpretation would be helpful. However, opinions diverged over the content of such guidelines or standards. One participant stated:

“We have to be careful when talking about guidelines. We need to be specific about the type of testing that is going to be appropriate under different circumstances, without being so specific to say what you must do. Because number 1, that will timestamp our recommendations and not allow innovation to happen if something more effective comes along. Number 2, it would undermine those who are leading the investigation, and who will be working in the labs to use their best judgment of what is going to be the most appropriate under the circumstances.”

Thirteen participants stated gold standard methodologies should be identified and any investigation should prioritize these methodologies over others, with some also suggesting further methodologies (such as those on the cutting edge) could be used alongside the gold standard methods. Other participants felt no cutting-edge methodologies should be used because they might risk producing results that are not well understood, creating room for questions and doubts. Eight participants suggested that instead of listing methods that should or should not be used in an investigation, having the international community agree upon and create parameters for selecting or modifying protocols for evidence analysis prior to an investigation would be useful. Additionally, 33 participants supported the development of guidelines on how to

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demonstrate and report validation of methodologies, including appropriate controls, would be helpful.

In addition to the breadth of protocols for sequencing and other evidence analysis steps, there exist many options for bioinformatic analysis. Typically, scientists conducting analyses must decide on the parameters to include in a model, values for said parameters, methods of cleaning data, and many other decisions. Changes to any of these aspects can produce different results. Some participants highlighted the diversity of choices available for analyzing data as a key area needing assessment and said decisions made regarding these methods prior to the start of an investigation could alleviate wide disagreement concerning these ideas, even among the scientific community. Some expressed a desire reach more clarity and agreement on which parameters, models, and databases could be used in an investigation now, prior to an investigation. There were concerns about forfeiting data and data security if an investigation used previously published information, such as using common genome repositories for assessing possible natural origins of an agent.

Multiple participants noted that due to the sensitive nature of an attribution investigation, there will be people looking to discredit the process; therefore, it is of utmost importance that those wishing to discredit the investigation are unable to point to the investigation's science to achieve their goals. Highlighting the importance of appropriate analysis and reporting of results, one participant stated, "If the science is wrong, if the science is reported misleadingly, if the report overstates the science, the investigation is dead."

Weighing Evidence. Understanding how people weigh different types of evidence and how that weighting impacts interpretation and evidential conclusions is of great importance for informing future biological event investigations. Not all evidence is equally informative; direct evidence is stronger than circumstantial evidence. More common criminal investigation evidence, like fingerprints or surveillance footage, may be more readily accepted and understood by the public compared to evidence collected using more unfamiliar and complex methods. This could lead to more familiar types of evidence being more heavily weighted, even if it is less direct evidence. Such a situation

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risks that incorrect conclusions could be made and lead to harmful consequences, such as enabling discrimination or allowing a state to exploit geopolitical vulnerabilities.

Participants were asked what factors they considered when comparing different types of evidence. Most participants could not cite inherent qualities that made them value one type of evidence, such as biological samples, over another, such surveillance footage. Rather, participants named the source of the information or evidence as the top characteristic, followed by validation (controls used in tests, proof the methods were validated against other methods, etc.). The source of the evidence often was described as the most important attribute because "if the source isn't broadly trustworthy, its junk." Nearly all participants who ranked trustworthiness of sources/collectors of evidence during their interview (a total of 17) ranked them as follows: investigatory team, United Nations agency, well-respected international nongovernmental organization, national health or public health agency, local healthcare provider or clinic, military, national law enforcement, and local police. The first four sources, in the order listed here, were the same for all 17 participants who offered a ranking of sources. For 14 of the 17 participants, national health or public health agency ranked above military, national law enforcement, and local police. For the remaining three participants, national-level authorities or organizations ranked above local.

Some participants discussed difficulties with trusting evidence collected from law enforcement compared to public health or medical providers. While law enforcement was widely considered to have the experience and expertise to collect evidence, some participants stated they were less likely to trust evidence from law enforcement or military because such organizations were perceived to be more likely to be biased than public health or medical practitioners. Additionally, some participants said their ranking of sources' trustworthiness may change depending on the type of evidence or country in question. One participant said ranking sources for trustworthiness was impossible because different sources potentially could offer different types of evidence, and the trustworthiness of those evidence types could not be meaningfully separated from the trustworthiness of the source.

A majority of participants said they would be most convinced by a convergence of several different evidence types. For example, participants found that the strongest case

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for evidence results when multiple -omics methods, video surveillance, and intelligence signals all support the same conclusion. Participants were split on whether they would trust a conclusion drawn entirely from circumstantial evidence; 22 felt there must be biological samples to support a conclusion while others said there may be situations where they would have to trust results based entirely on circumstantial evidence because that may be all that is available. However, for those in the latter group, many stated epidemiological data and medical data at a minimum would be necessary if no biological samples were available.

When asked if there was a single piece of evidence that would be weighted most heavily, a few respondents said that a definitive delivery mechanism would be the most important evidence to them as it not only indicates if a biological event has happened but also indicates intent. However, no participant felt that identification of a delivery mechanism alone could be used to conclude an event was deliberate in nature nor who (if anyone) was responsible for the event; they would still need to see several pieces of evidence supporting that conclusion to believe the event was deliberate.

Other than a delivery mechanism, the only other type of evidence participants named as the most impactful or important was genomic evidence. Many considered genome comparisons vital for biological events. One participant stated, “The only way to definitively state beyond a reasonable doubt that something is naturally occurring would be to find the exact genetic match in an animal somewhere. Even then, I would need to see evidence for how it jumped to humans. It’s not enough on its own, but it is the single most important piece if it can be done.” Phylogenetic analysis for tracing transmission or inferring evolutionary history was considered by some to be less impactful than direct comparisons of genomes. One participant noted that more models and assumptions are needed for phylogenetic analysis compared to matching genomes, thus weakening the level of certainty that could be derived from a phylogenetic analysis, which is why they considered the genome matching the most impactful analysis.

Addressing Uncertainty and Disagreement. Unlike other WMDs, biological agents can evolve and are ubiquitous in the environment with dynamic populations. Such characteristics mean that one sample taken at one time may not be identical to another

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sample taken in the future. Additionally, evolution is not predictable, and our current technologies are not capable of continuously monitoring or measuring microbial populations at the organism level. Rapid changes, limited resolution available to measure changes, and an inability to predict changes mean there are several ways in which uncertainty may be introduced into biological measurements.

In addition to the inherit uncertainty present in biology, there is uncertainty introduced through the methodologies for sample analysis (both physical lab methods and bioinformatics methods). The -omics methods likely to be used for attribution rely on statistics and report likelihood scores and/or confidence intervals, as these methods rely on assumptions built into the statistical method. Such uncertainty has complicated the use of genetic information in courtrooms in other types of cases.[xxi]

Participants agreed that, where possible, an investigatory team should take steps to decrease the uncertainty introduced in the investigation and be transparent about where uncertainty does exist. However, participants diverged in how they thought this would best be accomplished. Some participants said an investigatory team should quantify uncertainty within their investigation and results by reporting a number that expresses certainty in their result. Other participants said simply explaining where and why uncertainty exists would be sufficient to avoid unnecessary confusion. One participant went so far as to say that reporting a specific number for certainty would "be the downfall of the entire investigation." The scientific literacy of the audience was of concern to some participants, as many politicians who would be making decisions about what to do with the results of the investigation are not trained in science or statistics. They were concerned that a report too heavy with technical, scientific, or statistical detail would lead to confusion and make decision makers less likely to act on the results.

For many analyses done during an investigation, an investigatory team will need to rely on laboratory partners to assess the samples. Most participants who identified as scientists felt the laboratories and investigatory team should have a collaborative relationship, where laboratories have leeway to conduct experiments and different types of analyses as they see fit, since they are presumably the experts. Alternatively, many of the participants with expertise and experience working in international organizations

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stated that if laboratories were allowed to do anything other than what was directly stated by an investigatory team, the integrity of the investigation and evidence could be questioned.

Reporting Results

Participants frequently discussed the importance of having a strong strategy for communications with both politicians and the public. Many participants mentioned the importance of the investigatory team to not leak information via personal channels and to only speak to the media if authorized by the head of mission, as there needs to be very clear and structured messaging surrounding the investigation. Some participants warned that an attribution investigation is likely to spark mis- and disinformation. It was suggested that to combat the spread of false narratives, an investigatory team would need to include a highly trained spokesperson capable of clearly discussing technical details while also navigating the political environment. One participant felt this spokesperson role was the single most important position in the entire investigation.

Multiple participants noted that for any international investigation, there would be people who try to discredit and politicize the investigation, so the investigation must be technically sound and beyond reproach. Regarding the 2013 Syria investigation, one participant pointed out that critics accepted the science and technical information in the report but instead took issue with procedural aspects.[xxii] Additionally, the investigation must be scientifically sound, and all information presented as fact must be true, as just one mistake or false statement could be exploited to invalidate the entire endeavor.

COVID-19 origins discourse was frequently cited as an example of the incredible amount of mis- and disinformation that may circulate related to an investigation or attribution. Many participants felt any biological event, regardless of the type, origin of the agent, or amount of evidence, would be subject to at least some conspiracy theories, in part due to how intimately health threats affect individuals and societies. Participants who discussed mis- and disinformation often described a phenomenon where the amount of evidence publicly available would correlate to the quantity of mis- and disinformation and conspiracy theories. Events with little evidence—particularly those that most experts believe to be naturally occurring—were speculated to be highly

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vulnerable to disinformation. To prove something is not deliberate or accidental in origin, and thus naturally occurring, likely would require proving a negative. Alternatively, participants speculated that events that have large amounts of evidence would also be highly susceptible to an increase in conspiracy theories and mis- and disinformation. Events with plentiful evidence were believed to be vulnerable because those so inclined could create more narratives to promote falsely contradictory evidence or otherwise poke holes in official stories. While no participant suggested limiting the amount of evidence made available to the public, many expressed extreme concern over the potential misuse of evidence for such purposes and stressed the importance of a communications plan with considerations for dealing with mis- and disinformation.

Some participants noted that policy, social science, and communications experts on an investigatory team be integrated into writing the report. These participants noted that scientists often are trained to write for an audience of other scientists, who are not the sole audience of an investigation report. There was a division in how best to report results, primarily along disciplinary lines. People who identified as scientists often said reporting results should include a quantification of uncertainty or confidence in results, such as stating an exact percentage of confidence in different hypotheses covered in the report. People who self-identified as policy, legal, or international relations experts often said that having specific confidence numbers would create serious problems for those needing to act based on the report. These experts said instead of exact numbers, the report should be clear which results are ambiguous and use language that is clear about what is known or not known, without overstating what the evidence and subsequent analysis concludes.

Most participants felt it would not be possible to conclusively state the exact origins of an agent causing biological event. Rather, the goal should be a “convergence and preponderance of evidence that paints a picture” of what happened. There should not be an expectation that every piece of evidence will prove a theory or that any one piece of evidence alone will prove a theory. Instead, all the evidence should be considered together. There was wide acknowledgement among participants that interpreting evidence would be a challenging, “murky” process as many pieces of evidence, if considered individually, could be interpreted to support multiple different hypotheses. Cherry picking of evidence to support certain narratives is likely from those wishing to

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discredit the investigation or to support a specific agenda. The investigatory team cannot be seen as also cherry-picking evidence, least they risk undermining integrity and trust in the investigation. This drives the need for clear, transparent, and fact-based reporting of the results. Some said there could be temptation for an investigatory team to only present evidence that supports their proposed narrative but emphasized that evidence supporting all theories should be collected, analyzed, and reported.

Technologies to Enable Attribution

While there was no consensus regarding the likelihood of an investigation being successful in identifying a perpetrator, most participants felt the potential for success of attribution was increasing with technological advancements. In fact, many participants felt that technology was not a limiting factor for attribution; instead, legal, political, and social factors were considered greater barriers. One participant stated, “Science has advanced rapidly, and we are ready, but politics, laws, and policy hold us back.” High throughput -omics methods and computational advancements were the most mentioned technologies believed to contribute to increasing feasibility of attribution.

Genetic Technologies

Genetic sequencing was widely reported as vital for attribution of microbial agents. Using sequencing, investigators can identify the pathogen and look for signals that could point to origins of the agent. Having the genetic sequence of an agent enables investigators to make comparisons between samples collected as part of the investigation (such as samples collected from different victims or locations) or between a sample in evidence and sequences in repositories (such as Genbank or Addgene). Such comparisons are particularly helpful for assessing whether a common agent is causing disease, comparing evidential samples to environmental samples to assess the possibility of natural occurrence, and comparing samples gathered from victims to samples collected from laboratory or other spaces being investigated as potential origins. Genetic sequences also can be analyzed to consider genetic signatures that may indicate whether the agent was genetically manipulated; help delineate between a naturally occurring, accidental, or deliberate event; or provide information that may indicate if a particular laboratory supplied or manipulated the agent. Additionally, if the biological event is causing disease in multiple individuals, genetic sequencing information of the pathogen can be used for molecular epidemiology to better

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understand transmission patterns and evolutionary history, both of which could point to attribution.

Some participants also discussed the limitations of using genetic sequences for attribution. Genetic sequencing is useful for identifying pathogens but is not particularly useful for understanding functional differences, which contribute to pathogenesis and other signals that are used to monitor and categorize an event. Some participants mentioned that genetic sequencing often is cited as the primary data needed for attribution, but in practice, sequence data alone is insufficient for attribution. While genetic sequence information can be used to infer helpful information, such data has limited ability to demonstrate whether any intent underlies an event. Even if an agent is determined to be genetically modified, additional information would be needed to understand the motivation leading to such modification.

Participants were split about whether environmental surveillance for microbial agents would produce useful information for attribution. Environmental surveillance entails the broad collection of microbial agents in a given environment and cataloging results. Some participants felt this information could be used to compare with samples collected from an investigation site, to possibly identify a geographic location of origin. One participant mentioned that the practice of environmental surveillance alone could be useful as it could act as a deterrent; even if the information produced is not useful in an investigation, if potential adversaries think environmental surveillance produces useful information, it could decrease their interest in pursuing a bioweapon. Other participants felt that environmental surveillance would not be useful for attribution because investigators would have to be sampling constantly from all locations to have sufficient data to track an agent's origin. They argued that because biological agents evolve and microbial population structures can change frequently, one-time collection would have limited utility for attribution.

Other -Omics-Based Technologies

While genetic sequencing was the single most common technology reported as important for attribution, other -omics-based approaches, particularly transcriptomics

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and proteomics, were also regularly mentioned. Because these methods assess molecules that are directly involved in function of the agent, they can provide different information than genetic sequencing. Proteomics, for example, can provide signatures that indicate different pathways of pathogenesis or virulence between different strains.[xxiii] Similar to how genetic sequences can be used as comparators, protein signatures may also shed light on where or how an agent was created or manipulated, such as if it was cultured in a certain animal or cell line.[xxiv] Proteomic signatures may also help point toward intent or motivation, more so than genetic signatures, as proteomic signatures refer to a function or characteristic directly. In addition to proteomic signatures to assess identity or unique functions, some participants also mentioned using mass spectrometry for isotope analysis, which could provide information about the geographic location where an agent was created.

Computational Tools

Participants also frequently suggested computational tools for advancing attribution. Some participants mentioned the use of algorithms designed to identify potential source laboratories but with limited enthusiasm for their feasibility. Other computational tools that were suggested included programs that would comb through computer or institutional purchasing histories to look for evidence of malicious intent or abnormal behavior, programs to analyze social media histories looking for evidence of past locations or possible motivations, or programs that combine different types of data sources to assess behavioral patterns. As with the other technologies, computational tools were considered to have limitations. The most common mentioned was the reliance on quality data needed to develop and/or use such algorithms. There was doubt among some participants that the repositories used to collect sequence information would be sufficiently reliable for attribution given the relatively small sample size of data included in the repositories and lack of security measures protecting many public repositories. For other data sources, a few participants noted concerns about the depth of surveillance feeding such algorithms and the potential for invasion of privacy.

Conclusions

Understanding the causes of biological events is critical for preventing similar events in the future. Attribution serves as a deterrent for intentional misuse of biological agents, whereas identifying the origins of biological agents responsible for threating human,

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animal, or environmental health is critical for developing and implementing effective interventions to prevent repeat events. Developing clear guidelines and tools for investigation and attribution before they are needed is vital for their successful use during an emergency. Notably, however, efforts to identify a biological agent's origin likely will always be a sensitive exercise. There will be many nuances specific to each scenario. Stakeholder attitudes and opinions evolve over time, whether over the course of a single investigation or between events. Flexibility and adaptation are vital characteristics for all stakeholders, including investigators, those responsible for acting on the results of the investigation, and the public.

There must be more clarification about what policies and pathways are available for international investigations. Clarifying what agencies have authority to investigate different types of events, especially those ambiguous in nature, is an immediate priority. The WHO, in particular, requires clarity about at what point they are not responsible for investigating a disease outbreak and at what point another entity, and which one, will take over an investigation. Clarifying who has the authority and responsibility to conduct investigations is not only a logistical imperative. Leading or even participating in an investigation can leave an organization vulnerable to mis- and disinformation and other attacks that could degrade public trust in the organization. For entities like the WHO, whose mission in the public health space is dependent on trust from governments and the public, participating in an investigation has potentially grave consequences that could impede its ability to fulfill its mission. Certain nongovernmental organizations that provide healthcare or other necessities could similarly be blocked from continuing to provide aid if they participate in an investigation or provide samples or evidence. Such groups require more clarity on what they are legally obligated to do to develop their own policies and procedures for investigations.

There should be an international effort to gain consensus on methodologies widely accepted in an investigation. Even without consensus on all types of methods that could be used, identifying gold standard methods that could be used to validate new methods would be useful. When seeking such consensus, there must be representation from multiple disciplines and nationalities for the results of such work to be acceptable and fair. Ensuring any established guidelines on analysis techniques and investigatory protocols are accepted and validated across stakeholders and regions is critical. If a

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country or other entity criticizes an investigation based on its methods or conduct, having broadly endorsed or accepted standards will help to protect the results. Additionally, standards can help an investigatory team make decisions, rather than having to guess acceptable or best options. Additionally, guidelines about communication strategies, including how to manage mis- and disinformation, are important. As new technologies are developed and become available, stakeholders should regularly review advances to determine any alterations in protocol.

The science and technology of biological event attribution investigations are solid, but policy, political, and implementation barriers are inhibiting this work. Understanding expectations is the first step in creating a usable and viable attribution framework. Developing a playbook for attribution could help identify areas of uncertainty and necessary research, such as assessing how different types of evidence are interpreted and how the factors identified in this paper may influence decision making and action following an investigation.

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