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Importance of diagnostics in epidemic and pandemic preparedness

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ABSTRACT

Diagnostics are fundamental for successful outbreak containment. In this supplement, 'Diagnostic preparedness for WHO Blueprint pathogens', we describe specific diagnostic challenges presented by selected priority pathogens most likely to cause future epidemics.
Some challenges to diagnostic preparedness are common to all outbreak situations, as highlighted by recent outbreaks of Ebola, Zika and yellow fever. In this article, we review these overarching challenges and explore potential solutions. Challenges include fragmented and unreliable funding pathways, limited access to specimens and reagents, inadequate diagnostic testing capacity at both national and community levels of healthcare and lack of incentives for companies to develop and manufacture diagnostics for priority pathogens during non-outbreak periods. Addressing these challenges in an efficient and effective way will require multiple stakeholders—public and private—coordinated in implementing a holistic approach to diagnostics preparedness. All require strengthening of healthcare system diagnostic capacity (including surveillance and education of healthcare workers), establishment of sustainable financing and market strategies and integration of diagnostics with existing mechanisms. Identifying overlaps in diagnostic development needs across different priority pathogens would allow more timely and cost-effective use of resources than a pathogen by pathogen approach; target product profiles for diagnostics should be refined accordingly. We recommend the establishment of a global forum to bring together representatives from all key stakeholders required for the response to develop a coordinated implementation plan. In addition, we should explore if and how existing mechanisms to address challenges to the vaccines sector, such as Coalition for Epidemic Preparedness Innovations and Gavi, could be expanded to cover diagnostics.

Summary box

- Diagnostics are a fundamental component of successful outbreak containment or control strategies, and each individual pathogen presents specific diagnostic challenges. Current diagnostic landscapes for selected priority pathogens are presented in this supplement.
- Recent outbreaks of Ebola, Zika and yellow fever have highlighted overarching barriers to diagnostic preparedness that are common to all outbreak/epidemic situations.
- A holistic, multistakeholder response through healthcare system strengthening, improved market sustainability and integration of diagnostics into existing preparedness mechanisms for vaccines is recommended to address these barriers and create a comprehensive overall epidemic and pandemic preparedness plan.
- Identifying overlaps in diagnostic development needs across different priority pathogens is recommended over a pathogen by pathogen approach to allow more timely and cost-effective use of resources.

INTRODUCTION

Diagnostic tests are a fundamental component of a successful outbreak containment strategy, being involved at every stage of an outbreak, from initial detection to eventual resolution.[1–3] Development of diagnostic tests suitable for epidemic prevention and containment is technically challenging, and processes for development, validation and implementation are complex and time consuming. The WHO R&D Blueprint for Epidemic Preparedness lists those pathogens thought most likely to cause a future epidemic,[4] but while diagnostic tests exist for the majority, availability is often poor at central laboratory level, and many tests are not available in a format that can be deployed at a community level (table 1).[5]

Poor diagnostic preparedness has contributed to significant delays in the identification of recent outbreaks for multiple pathogens, including Ebola,[2] Lassa fever,[6] yellow fever[7] and Zika,[8] primarily due to poor local diagnostic capacity. In the case of the 2013–2016 Ebola epidemic in West Africa, there was a 3-month delay between the index case and the identification of the causative agent; postoutbreak analyses suggest that diagnosing 60% of patients within 1 day instead of 5 days could have reduced the attack rate from 80% to nearly 0%.[2 9] In the end, it was diagnostics

Table 1 Six of the 10 WHO Blueprint priority diseases have significant diagnostic gaps

WHO Blueprint priority disease[4]	Fatality rate	Recent outbreaks	Diagnostic need (red: critical, yellow: important; green: unaddressed)*[5]	Situation overview[5]
CCHF	10%–40%[38]	Pakistan, 2010.[39]		► No established reference test. ► Very limited availability of commercial assays, with very low usage and limited performance data. ► No WHO prequalified diagnostic test.
Filoviruses (Ebola and Marburg)	24%–90%[40 41]	West Africa, 2013–2016 and DRC 2017 and 2018 (Ebola).[10] Uganda and Kenya, 2017 (Marburg).[42]		► Recent high-profile outbreaks resulted in international focus and funding, which has enabled the development and introduction of critical diagnostics. ► Additional work is needed to improve current diagnostics, develop POC tests and ensure reliable availability. ► Additional work is also needed to ensure regulatory approval beyond WHO EUAL.
Lassa fever	1–15%[43]	Annual recurring outbreaks in West Africa.[44]		► No WHO-approved diagnostics and limited commercially available tests, none of which are easily deployable in the settings needed.
MERS-CoV	~35%[45]	Saudi Arabia, 2013–2018. South Korea, 2015.[46]		► Limited availability of validated assays, restricted to highly complex tests. ► Lack of POC diagnostics.
SARS	~10%[47]	Global, 2003.[47]		► Recent high-profile outbreaks resulted in international focus and funding, which has enabled the development and introduction of critical diagnostics. ► Additional work is needed to improve current diagnostics, develop POC tests and ensure reliable availability.
Nipah and henipaviral diseases	~30%[48]	Bangladesh, 2004.[49] India, 2018.[50]		► No WHO-approved diagnostics and limited commercially available tests, none of which are easily deployable in the settings needed.
Rift Valley fever	<1%[51]	Republic of Niger, 2016.[51]		► No WHO-approved diagnostics and limited commercially available tests, none of which are easily deployable in the settings needed.
Zika virus disease	Not fatal[52]	South and North America, 2015–2016.[29]		► Recent high-profile outbreaks resulted in international focus and funding, which has enabled the development and introduction of critical diagnostics. ► Additional work is needed to improve current diagnostics, develop POC tests and ensure reliable availability. ► Additional work is needed to ensure regulatory approval beyond WHO EUAL.
Disease X				► Need for diagnostic platforms that can rapidly adapt and support diagnostics for unknown pathogens.

*Red/critical: diagnostics needed but not currently available or validated; yellow/important: diagnostics currently under development; green/unaddressed: diagnostics available but may need improvement.
CCHF, Crimean-Congo haemorrhagic fever; EUAL, Emergency Use Assessment and Listing; MERS-CoV, Middle East respiratory syndrome coronavirus; POC, point of care; SARS, severe acute respiratory syndrome.

information coupled with appropriate interventions that led to eventual containment of the outbreak, but the delays resulted in the loss of thousands of lives and billions of dollars in the cost of response.[10 11] While improvements in availability of point-of-care diagnostics and a more rapid set up of laboratory facilities in transmission zones limited the spread of the April 2018 Ebola outbreak in the Democratic Republic of Congo,[12 13] logistical issues with delivery of supplies and shortages of experienced staff persisted.[14]

Table 2 Key challenges to diagnostic preparedness and potential solutions

Challenges	Proposed solutions
Research and development	
Lack of diagnostics in a format adapted for field use	► Develop comprehensive diagnostic platforms that can rapidly adopt new assays to build sustainable capacity at country level. ► Develop diagnostics with limited sample preparation and training needs.
Insufficient funding and lack of coordination between donors leading to duplication of effort	► Establish coordinating body for diagnostics funding. ► Match small start-up companies/academia with larger diagnostics or vaccine/pharmaceutical manufacturers with greater capacity.
Poor commercial viability of diagnostics during non-outbreak periods	► Provide market incentives for manufacturers and establish sustainable business models to offset losses during non-outbreak years. ► Provide funding for stockpiling of tests.
Limited access to samples leading to further delays in diagnostic development	► Establish a specimen sample bank, open to both the diagnostics and vaccines industries, including storage locations and processes for access.
Limited collaboration between experts and laboratories with pathogen-specific expertise	► Expand networks of expert personnel and laboratories to allow more rapid responses during outbreaks and maximise knowledge sharing. ► Partner diagnostics and vaccine developers to find novel diagnostic targets.
Delays in sharing of diagnostic data affecting response and containment times	► Create connectivity solutions enabling real-time data reporting.
Logistical and healthcare system preparedness	
Shortages of diagnostic materials and supply chain interruptions during outbreaks	► Preselect suppliers to ensure appropriate capacity for outbreak situations. ► Establish manufacturing lines for diagnostic production during outbreaks.
Poor diagnostic and surveillance capacity at national level in many countries	► Reinforce surveillance capacities through implementation of surveillance laboratory networks, adapted to specific country needs, or transformation of surveillance laboratories for routine testing. ► Educate healthcare workers on the importance of real-time reporting. ► Link diagnostics and vaccines in a common health programme. ► Adopt a 'One Health' surveillance approach that integrates human, animal and ecological health.

It is vital that the current lack of rapid diagnostic tests for priority pathogens is addressed, to ensure that future outbreaks can be more effectively contained. Detailed descriptions of the diagnostic landscapes for selected WHO R&D Blueprint pathogens are provided in this supplement.[15–19] Each of these pathogens presents specific challenges, due to differences in factors such as geographical location (Nipah infection primarily occurs in Asia, Middle East respiratory syndrome-coronavirus (MERS-CoV) in the Middle East and Lassa fever in Africa, while Crimean-Congo haemorrhagic fever (CCHF) is widespread) and mode of transmission (MERS-CoV in particular has a significant animal reservoir in dromedary camels, while CCHF is a tick-borne disease), among others. However, there are a common set of barriers to effective deployment and utilisation of diagnostic tests. In this article, we consider these overarching challenges to diagnostic preparedness and offer potential solutions (table 2), looking to existing systems already in place for vaccines preparedness for guidance.

CHALLENGES TO DIAGNOSTIC PREPAREDNESS

Research and development challenges

Poor diagnostic capacity at national and community levels of healthcare can greatly reduce the effectiveness of outbreak containment, as demonstrated by the recent yellow fever outbreak in Central Africa in 2016–2017.[7] The yellow fever virus is endemic throughout Africa, and an effective vaccine has been available for almost 80 years; nevertheless, the outbreaks in Angola and Nigeria in 2016–2017 were not well prepared for.[20] While detection of yellow fever in serum using ELISA is technically possible at national level, there was a severe shortage of reagents, meaning that laboratories were unable to carry out tests on the majority of suspected cases.[7] Confirmatory antibody neutralisation testing could only be performed at a single central reference laboratory in Senegal (Institut Pasteur, Dakar; the only centre in Africa equipped for this), which can take up to a month, including time required to transport samples and receive testing results. This caused significant delays in recognising the outbreak, hindering the roll-out of the vaccination programme and diminishing the effectiveness of targeted vaccination, resulting in increased spread of disease and longer time to containment. The reagent shortage continued throughout 2016 and the first 8 months of 2017, and by the time the required reagents became available at national level, the disease had spread to multiple states.[7] Improved access to rapid tests to speed up diagnosis of patients presenting to triage tents was badly

needed. During the Ebola outbreak in early 2018, although availability of point-of-care testing and of testing facilities in transmission zones has been much improved,[12 21] a delay in detection of initial cases and a lack of good epidemiological information has presented difficulties in estimating the true geographical extent and magnitude of the outbreak.[13]

The key lesson from these experiences is that diagnostic tests in a format adapted for field use are essential for rapid containment of outbreaks, even in the presence of an effective vaccine. This lack of affordable and definitive diagnostics has been described as one of today's most serious health security blind spots[7] and will be of particular importance for outbreaks that tend to occur in rural locations, such as Lassa fever, and those that primarily affect mobile populations, such as MERS-CoV.[18 19] While general infrastructure strengthening and capacity building is essential and will bring rapid improvements to diagnostic preparedness (see next section), creation of sustainable programmes for disease surveillance in low-income countries can only be achieved through the development of innovative diagnostic technologies that can be made affordable and available. One approach to building sustainable facilities at country level is the development of flexible diagnostic platforms that can rapidly adopt tests for different pathogens. Multipathogen panels are particularly valuable for initial detection and monitoring of outbreak-causing pathogens, allowing rapid response without undue taxing of human resources through diversion of attention from other tasks, additional training requirements or need for implementation of new supply chains.[22] Additionally, diagnostics that require limited sample preparation would reduce training needs and minimise the risk to laboratory workers, and so would be particularly advantageous for pathogens that are easily transmittable and/or cause severe disease. Indeed, the delay between the index case and the identification of Ebola as the causative agent during the 2013–2016 Ebola epidemic was partially due to a lack of appropriate high-level containment facilities at the lower levels of healthcare, meaning that samples had to be sent to a central laboratory.[2]

The provision of funding for the development of critical pathogen-specific assays that can be employed in a decentralised setting is essential to address the current gap in diagnostic epidemic and pandemic preparedness. However, funding must be sufficient, and its allocation must be strategic and coordinated. During the 2013–2016 Ebola epidemic, substantial public funding (approximately US$ 435 million) was made available from various governmental, public and philanthropic sources,[23] but this was distributed across multiple recipients, many of them small start-up companies, through a series of relatively small 'panic grants'.[2] Of these 70 companies, few were capable of success. They often lacked the resources and infrastructure to complete product development as well as the manufacturing and distribution capacity to meet demand had they received product approval. Although seven companies eventually earned WHO Emergency Use Assessment and Listing approval[24] and 11 earned US Food and Drug Administration Emergency Use Authorization approval for their tests,[25] the delays and inefficiencies introduced by the fragmented funding process demonstrates a need for improved coordination for future outbreaks and the importance of ensuring that funding is allocated to companies with sufficient capability and resources.

The Coalition for Epidemic Preparedness Innovations (CEPI) is an alliance that raises and coordinates funding for development of vaccines for epidemic-causing pathogens; leveraging a similar mechanism for diagnostics would help to prevent the issues seen during the Ebola epidemic. Coordination between funding recipients as well as donors would also be beneficial, for example, matching up a smaller set of start-up companies or academic bodies with relevant expertise to larger manufacturers with greater capacity and resources would ensure more efficient use of funding and technical synergies to accelerate the diagnostic research and development pathway to market.

The commercial viability of diagnostics during non-outbreak periods is another important issue that needs to be addressed, as a lack of market incentives as outbreaks decline discourages companies from continuing development and commercialisation. Of the companies that participated in diagnostic development during the recent Zika epidemic, the majority are no longer continuing research now that the outbreak is over. Innovative financing solutions, including sustainable market commitments, pooled procurement mechanisms and funding for stockpiling of tests, must be put in place to establish a sustainable supply chain and support long-term commitments from manufacturers by offsetting currently unsustainable losses during non-outbreak years. Notably, mechanisms are already in place to address some of these challenges in the vaccines sector, for example, processes established by Gavi, the Vaccine Alliance, have proven highly effective in ensuring supply of vaccines during outbreaks; similar mechanisms should be explored and tailored to the diagnostics market.[26]

In addition to the lack of coordinated funding, research and development of diagnostic tests for recent outbreaks has been hampered by insufficient access to well-characterised, good quality, validated specimens.[2 27 28] During the Zika outbreak in South America and the USA in 2015–2016, despite requests for diagnostics from affected countries, poor access to samples and other reference materials, in part due to export restrictions, greatly delayed the development of diagnostic tools.[29] This delay in turn prevented timely and accurate Zika case confirmation and delayed generation of the scientific evidence needed to confirm the suspected relationship between the increase in severe neurological complications and Zika infections. Diagnostics developers had to purchase specimens without guarantee of the quality of the clinical characterisation (which is of particular importance for the Zika virus due to the high immunological cross-reactivity with dengue virus and other flaviviruses).[30] Efforts to validate

diagnostic tests for the WHO R&D Blueprint pathogens CCHF and MERS-CoV have also been hampered by difficulties with sourcing of clinical specimens, as described elsewhere in this supplement.[15 18]

The establishment of a specimen sample bank, in the form of an online sample repository, would help to ensure that development for future outbreaks proceeds in a more timely and transparent manner and would allow for quality guarantees. In addition to providing information on specimens collected, ideally, this repository would also include storage locations and processes for access. A shared system open to both diagnostics and vaccines industries would ensure optimum efficiency. An example of an effective sample sharing initiative is the Pandemic Influenza Preparedness Framework, founded by WHO after the 2009–2010 H1N1 influenza pandemic, which establishes sharing agreements with industry partners involved in the WHO Global Influenza Surveillance and Response System, whereby WHO provides strain samples and industry stakeholders commit to provision of vaccines and diagnostics.[31]

Effective collaboration and communication between experts and laboratories with pathogen-specific expertise is also essential to the rapid development of diagnostic tests. During the H1N1 influenza pandemic of 2009–2010, existing networks of subject matter experts and expert laboratories, established for the purposes of seasonal influenza surveillance, were able to quickly respond to the outbreak, enabling early detection of the emergent strain,[32] rapid implementation of containment measures and adaptation of existing surveillance programme to monitor spread. Diagnostic expertise was particularly important in this case, as the pandemic strain had to be detected against a background of other circulating influenza A strains and other respiratory viruses causing influenza-like illness.[32] The influenza example demonstrates the positive impact that collaboration between global and national stakeholders and industry can have on the speed and effectiveness of response. Similar networks of diagnostic experts and laboratories for other relevant pathogens that can be activated in the event of an outbreak would greatly improve research and development times. Both academic and private sector stakeholders would be included with a focus on maximising knowledge sharing and accelerating innovation, in an environment that encourages collaboration rather than competition between developers. Partnering with vaccine developers to find novel diagnostic targets is also strongly recommended, as vaccine developers must conduct extensive research into the immune response to pathogens. An example of how effective this could be is provided by the rk39 ELISA test for detection of visceral leishmaniasis, which was developed by the Infectious Disease Research Institute in Seattle as a by-product of their vaccine research.[33]

Improvements in the sharing of diagnostic data would greatly improve the diagnostic response to outbreaks. During the 2013–2016 Ebola epidemic, delays in sharing of diagnostic data affected containment times. Variations in reporting practices, non-governmental organisations keeping data private, long delays in release of data from academic institutions and a failure to link West Africa's surveillance to international systems all led to data fragmentation and inconsistencies that impacted the effectiveness of the containment response.[34] Some improvements were seen during the Zika outbreak, with an agreement among journal editors to allow rapid publication of outbreak data.[35] In addition to this, linking diagnostic tests with communications technology enabling real-time data reporting and transmission of geo-tagged test results to national and international health information systems would facilitate improved tracking and mapping of geographical patterns, allowing for faster response and containment as well as improved supply chain management.

In cases where diagnostics have not been developed in advance of an outbreak, the Ebola and Zika experiences highlight the importance of ensuring that the development process is condensed as much as possible. During the 2009–2010 H1N1 influenza pandemic, utilisation of processes for emergency use authorisation of diagnostic devices allowed development and approval of new platforms to be accelerated, with several new diagnostics gaining authorisation for use in detection of the pandemic strain (the majority of these were reverse transcriptase PCR based).[32 36] The availability of these assays provided substantial surge capacity, and as some were designed for use on existing platforms, expenses for laboratories already equipped with these platforms were minimised.[36] Expedited regulatory approval processes are therefore important to enable diagnostic tests to be brought into use as rapidly as possible after the initial development stage. However, mechanisms to approve such tests for routine use after declarations of public emergency have been closed are lacking, particularly as emergency use approvals can be granted based on sparse data.

Logistical challenges and healthcare system preparedness

As discussed above, the recent yellow fever and Ebola outbreaks underline the impact of interruptions in supply on time to containment.[2 7] To prepare for future outbreaks, it will be important to ensure that sufficient manufacturing capacity for diagnostic tests is in place. Preselection of suppliers to manufacture diagnostic tests for priority pathogens would ensure that companies that already have appropriate manufacturing capacity are enlisted to supply diagnostics during an outbreak scenario, but additional investment in manufacturing will be essential to allow urgent demands to be met without negative impact on other business commitments. Establishment of manufacturing lines specifically for the production of diagnostics for current outbreaks would help to guarantee sufficient supply and would offset costs for manufacturers who would otherwise need to stop

production of other higher income-generating products to respond to a global health emergency. These manufacturing lines could be funded, for example, by a number of government donors; an overarching decision-making board to manage investments and prioritise products for manufacture would of course be required.

Overall strengthening of the diagnostic capacity of laboratories at national levels is important for any preparedness strategy. Reinforcement of surveillance capacity of weaker healthcare systems, including education of healthcare workers and implementation of surveillance laboratory networks, is critical to allow earlier identification of outbreaks and more effective isolation of cases. The influenza pandemic of 2009–2010 shows how effective a robust global surveillance network can be[32]; in particular, the mentoring system that was employed to provide support for countries with lower technical abilities from those with stronger diagnostic capacity was a successful measure that could be implemented for other pathogens. In contrast, the recent yellow fever and Zika outbreaks clearly demonstrate the negative impact of poor surveillance.[7 8] The absence of a specific marker for Zika surveillance was largely responsible for the wide spread of the disease, as without surveillance information, effective control measures could not be put in place.[8] The disconnect between surveillance findings and provision of vaccines negatively impacted the containment response to the yellow fever outbreak.[7] Ensuring that national-level laboratories are equipped to test for a wide range of diseases and that they work in interconnected diagnostic networks would significantly improve epidemic containment times, and the ability to transform surveillance laboratories for routine testing in outbreak situations would also relieve pressure on testing centres. Linking diagnostics and vaccines in a common health programme would help to ensure that vaccines are delivered in a timely manner to the most at-risk populations. For pathogens with significant animal reservoirs, such as the Nipah and CCHF viruses, collection and integration of animal surveillance data may also be a necessary component of any outbreak preparedness strategy.[15 17] A ‘One Health’ approach to surveillance that integrates human, animal and ecological health would provide earlier opportunities for outbreak detection and prevention; however, a number of challenges to implementing such an approach exist, including need for greater cross-sectoral communication, strengthening of laboratory networks, restructuring of existing systems, and development of shared databases, shortage of experienced personnel and limited availability of diagnostic tests suitable for animal use.[37]

NEXT STEPS: IMPLEMENTING THE PROPOSED SOLUTIONS

Taking a holistic approach to diagnostic preparedness will require a multistakeholder response. The first step may be the assembly of the multiple key stakeholders in this field to convene a global diagnostics forum. Bringing together all relevant parties, including industry (both diagnostics and vaccines, and large and start-up companies), WHO, other healthcare bodies such as the Unicef, Gavi and the Foundation for Innovative New Diagnostics (FIND), governments and subject matter experts, will allow for more efficient and productive discussions to determine the right solutions and how best to implement them, and could inform the development of new target product profiles that align with this comprehensive approach. This global forum approach has been commonly used in the vaccines sector in isolation (meetings of the CEPI forum and Joint Coordination Group are key examples), but no such meeting for diagnostics or the combination of diagnostics and vaccines has taken place.

Beyond enabling a multistakeholder engagement plan, there may be opportunities to leverage mechanisms in place to help address outbreak preparedness challenges in vaccines. Expanding these mechanisms to include diagnostics would be more efficient, making use of existing expertise and processes, and would allow for a more integrated approach to outbreak preparedness linking both diagnostics and vaccines, which are inherently connected. CEPI could act as a bridge between diagnostics needs and vaccine preparedness for research and development, and Gavi could dedicate resource to help generate market predictability. In fact, Gavi is already exploring how to best use its resources to enable more effective vaccine campaigns for yellow fever outbreaks through support of diagnostics. Moreover, FIND is already working with CEPI to ensure that diagnostics that can generate reliable surveillance data are available for priority pathogens including Lassa fever, Nipah, CCHF and Ebola, which will lead to accelerated vaccine development, evaluation and implementation. An exploration of lessons learnt from both of these experiences would be an appropriate topic for the first global forum.

CONCLUSION

Recent outbreaks of pathogens such as Ebola, Lassa fever, yellow fever and Zika viruses have been exacerbated by the lack of accessible diagnostic tests, leading to poor detection and surveillance, ultimately delaying the time to containment. While each pathogen presents specific challenges, several common themes have emerged from these cases that are applicable to all outbreak situations. In order to achieve a state of preparedness for future outbreaks of these pathogens, and of other potential epidemic-causing pathogens such as those listed in the WHO R&D Blueprint, there is an urgent need for overall strengthening of the diagnostic capacity of healthcare systems, and for financial and technical support mechanisms to be put in place to enable the timely development of innovative tests and to guarantee market sustainability. Funding should be prioritised to ensure that there is adequate investment in systems strengthening, since this will provide greater value for money in terms of overall

outbreak preparedness than focusing on individual pathogens. Similarly, target product profiles for new priority pathogen diagnostics should take these needs into consideration to ensure that maximum benefits to overall outbreak preparedness are derived from any new developments in the diagnostics field.

In conclusion, the importance of diagnostics in epidemic preparedness cannot be underestimated. Integration of diagnostics into existing preparedness systems and overall strengthening of healthcare system diagnostic capacity will lead to more rapid containment of future outbreaks, with the potential to save many lives and substantially reduce the healthcare burden.

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