



Target Product Profiles for improved antimicrobial stewardship for gonococcal infection



Background

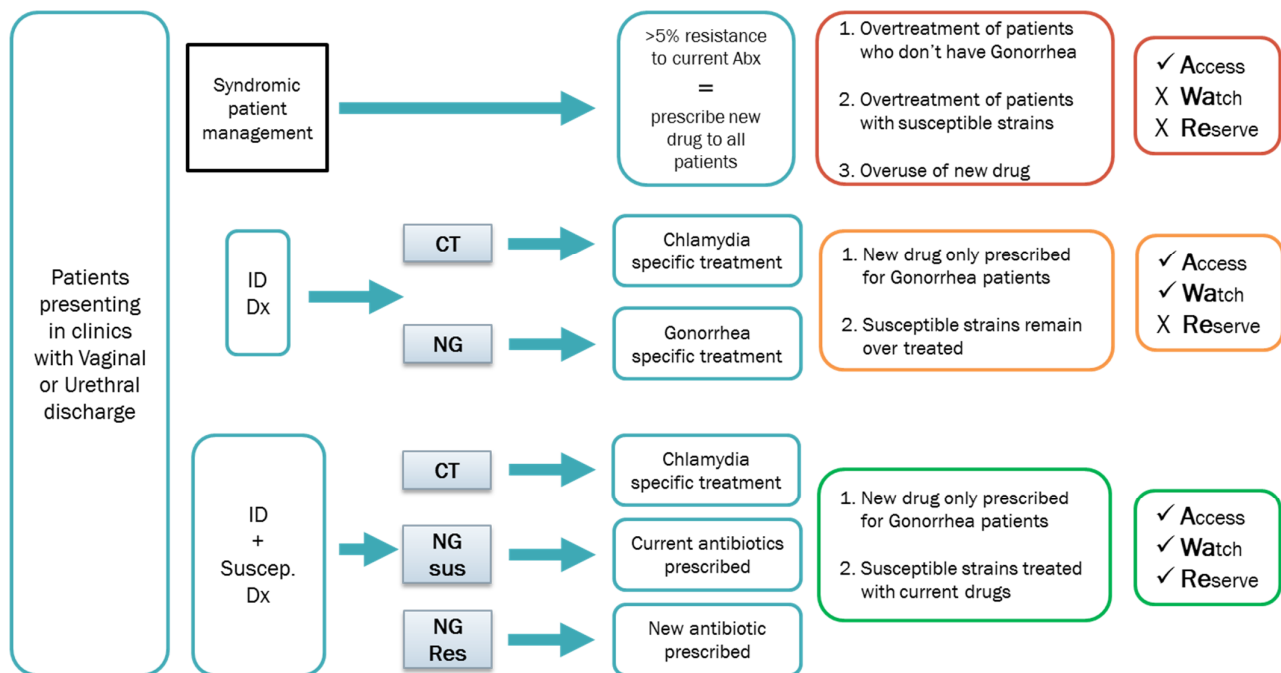
Gonorrhoea is the second most common bacterial sexually transmitted infection (STI) and results in substantial morbidity and economic cost globally.^{1,2} The WHO estimates that in 2016, 87 million new cases occurred among adolescents and adults aged 15–49 years worldwide with a global incidence rate of 20 per 1000 females and 26 per 1000 males, with the highest magnitude in WHO Western Pacific and African Regions. Co-infection with chlamydia (CT) is detected in 10–40% of people with gonorrhoea (NG).

The WHO has identified NG as a high-priority pathogen because of widespread antimicrobial resistance (AMR) to penicillin, tetracyclines, macrolides (including azithromycin), sulphonamides, trimethoprim, and quinolones, including emergent resistance to the “last line” extended-spectrum cephalosporins (ESC) cefixime and ceftriaxone. The emergence of decreased susceptibility of *N. gonorrhoeae* to ESC together with already-existing AMR to other antibiotics, make *N. gonorrhoeae* a multidrug-resistant organism. New therapies have been spearheaded by investments into the Global Antibiotic Research & Development Partnership (GARDP) and CARB-X. GARDP has prioritized the development of a new gonorrhoea antibiotic (Zoliflodacin) for the treatment of uncomplicated gonorrhoea, by 2023. As multiple organizations drive to develop new drugs, and WHO simultaneously recommends the AWARE (Access, Watch, and Reserve) approach for antibiotic stewardship, countries will need diagnostic tools to guide treatment choices, ensure current therapies remain effective for as long as possible and preserve new drugs from rapid development of resistance by overuse (Figure 1)¹.

Currently, there is no clinically validated rapid diagnostic test (RDT) widely available for NG identification. One FDA-approved molecular diagnostic test is available to distinguish between CT and NG infections; however, turnaround time to results is too long for use in clinics, the cost remains prohibitive for use in primary health care settings, and uptake remains limited to reference-level laboratories.⁸ Recent technology advancements may facilitate development of RDTs for NG. A low-cost rapid diagnostic test for NG detection alone or combined NG/CT detection and differentiation would enable wide scale uptake at primary health care level in LMICs.

New diagnostics are needed to help guide diagnosis and treatment decisions to foster antibiotic stewardship of existing and new antibiotics. If syndromic evaluation remains the primary approach to guide treatment of STIs, there is a significant risk of misdiagnosis and antibiotic overuse, which has been shown to lead to antimicrobial resistance.^{5–7} To prevent misuse of antibiotics, a diagnostic-based stewardship strategy is urgently needed, particularly at primary health centres where patients present for treatment. The stewardship strategy must fit within a redefined, WHO-supported clinical algorithm that includes the use of diagnostics for patients presenting to primary health care settings.

Figure 1. Stewardship of new antibiotics with diagnostic-guided patient management



WHO AWaRe: Access, Watch, Reserve approach to antibiotic use

Target Product Profile Initiative

To support WHO and GARDP, in developing a stewardship plan for both current antibiotics and for new drugs such as Zoliflodacin, WHO and FIND have started developing relevant Target Product Profiles (TPPs) to define two critical diagnostics that will be needed to address point-of-care diagnosis of Gonorrhoea and susceptibility to existing recommended antibiotics.

The complexity of a single assay capable of distinguishing between Chlamydia and Gonorrhoea and simultaneously determining susceptibility to currently available antibiotics is very high. We expect that development times required for this assay will surpass the time frame for introduction of new assays prior to the release of new antibiotics. We also expect that the cost of this assay will be substantially higher than currently available diagnostics due to its complexity. In order to balance these complexities two TPPs have been drafted to support the development of three solutions:

1. A rapid, low-cost diagnostic to distinguish gonorrhoea from chlamydia infection at primary care. (RDT TPP) The intended use of this TPP is for improved patient case as a minimal requirement and optimally includes case screening.
2. A comprehensive test to distinguish gonorrhoea from chlamydia infection and identify susceptibility/resistance to antibiotics to treat gonococcal infection. (Comprehensive test TPP) The intended use is to define a test to determine antibiotic resistance of NG to guide prescription of current therapies and facilitate antibiotic stewardship
3. Longer-term solutions that will incorporate both tests into one assay.

Developing Target Product Profiles through a Delphi-like process

An overview of the entire TPP development process is summarized in Figure 2.

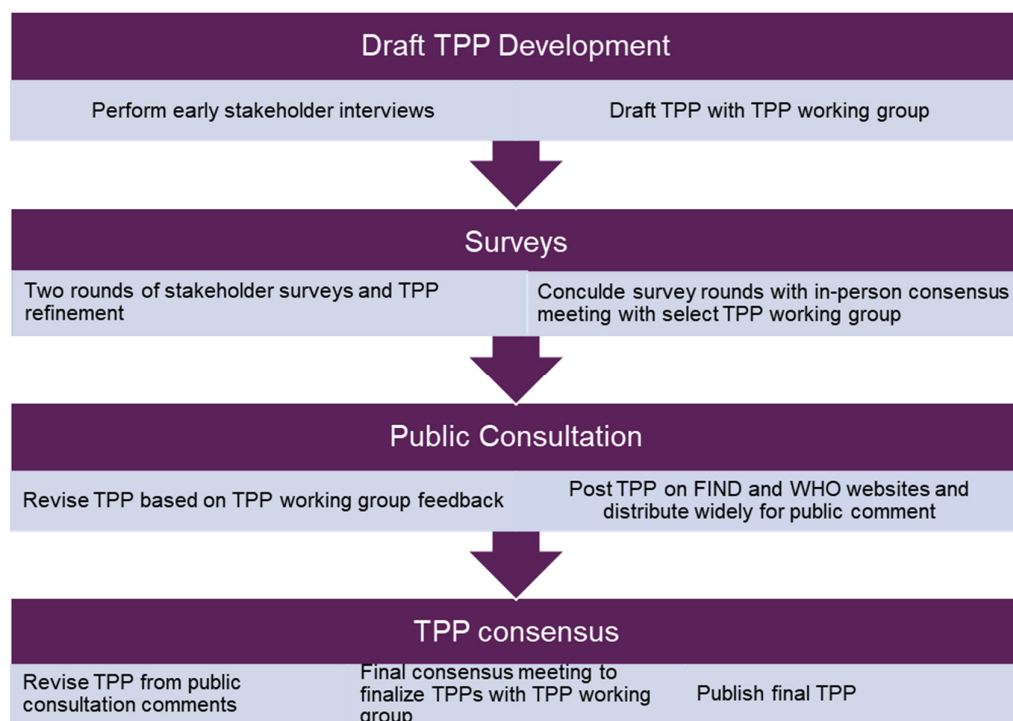


Figure 2: Overview of TPP Development Process

Draft TPPs were developed through interviews with opinion leaders and experts. To obtain consensus and arrive at final TPPs, a Delphi-like process was conducted that incorporated stakeholder input from 68 content experts. Stakeholders were surveyed electronically to obtain input on both TPPs. Survey participants were asked to rank their level of agreement based on a Likert scale ranging from 1 to 5 (1-disagree, 2-mostly disagree, 3-don't agree or disagree, 4-mostly agree, 5-fully agree). Individuals were asked to provide comments when they scored a characteristic at 3 or lower. Consensus was pre-specified as >50% of respondents agreeing with the proposed characteristics (Likert score of 4 or 5). A second level of consensus was evaluated at >75% agreement. Responses were analysed separately for industry and non-industry responses.

A TPP consensus meeting, co-hosted by WHO and FIND, was held on 5-6th of March 2019, in Montreux, Switzerland. This consensus meeting included a select group of experts with extensive and relevant field experience. TPP characteristics from the first Delphi survey that had lower levels of agreement (6 characteristics from the RDT TPP and 4 from the comprehensive tests TPP) were discussed. Survey comments were discussed and revisions to the TPP were drafted during the meeting and agreed upon by voting participants (n=16). Voting was based on a super majority, with a 70% threshold. During the consensus meeting, revisions to the TPP drafted in by meeting attendees and each proposed revision was voted on by participants. Full consensus was achieved on all but one characteristic, which exceeded the 70% super majority threshold with only one vote opposed.

Following the consensus meeting, the revised draft was sent for a second Delphi survey round and the survey process was repeated. Results from the second Delphi survey showed high levels of

agreement at the present agreement thresholds and no further revisions were made to the draft TPPs. The draft TPPs have undergone a second public consultation to solicit feedback prior to finalization. The proposed revisions were considered before the TPPs were finalized.

Conclusion

FIND, and WHO strongly believe that the development of concise and well-vetted TPPs can accelerate technological advances that will have a significant impact on the identification and treatment of Gonorrhoea infections. Co-development of the TPPs with WHO and FIND will ensure that countries will adopt the recommended policy changes as they begin to prepare for the introduction of the new antibiotics. FIND has launched a formal [Request for Proposals](#) with a draft TPP from interested industry partners to begin diagnostic development programs to ensure the prioritized diagnostics are available in time to meet the introduction timeline of new antibiotics (expected year of introduction for Zoliflodacin is 2023).