Annex 5.2

PICO 2 - Who to test (HCV)

Literature review on cost-effectiveness of HCV screening, treatment strategies and applicability to LMICs

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1. Executive summary
We conducted a targeted review of the literature to determine the state of evidence about the cost–effectiveness of testing for HCV in different types of epidemics and among different risk groups. We provide a qualitative assessment of conclusions.

5. Testing in high-risk groups such as persons who inject drugs (PWID), men who have sex with men (MSM), prisoners, HIV-infected persons, and commercial sex workers is likely to be cost–effective. Testing in settings with a high prevalence of high-risk patients is almost certainly cost–effective in all locations. It is important, however, to ensure adequate follow up after diagnosis.

6. The best approach to testing outside of high-risk risk groups depends a great deal on a country's unique HCV epidemiology. Most countries have at least some component of “birth cohort” epidemic, and “birth cohort” testing is likely cost–effective in most settings.

7. Routine testing of the entire population carries two risks. First, when the HCV epidemic is concentrated to a specific age or risk group, generalized testing can dilute the testing effort and reduce the number of HCV cases identified. Second, if an epidemic is highly concentrated with a specific risk or demographic group, screening outside of that group can be inefficient and increase cost. Countries with high HCV prevalence across the entire population should implement routine screening, but in most epidemics, routine screening in the entire population is likely not be cost-effective. The specific threshold at which a country should alter its approach to routine testing, however, is a function of multiple factors and cannot be identified more generally.

2. Background
Hepatitis C virus (HCV) is a global public health burden and major cause of morbidity and mortality including liver failure and hepatocellular carcinoma. Current global HCV seroprevalence is estimated to be 2.8%, or more than 185 million infected individuals worldwide. Historically, it has been very difficult to treat HCV and most cases of HCV have gone unidentified. The advent of high-efficacy, low-duration therapy, however, generates new enthusiasm for testing for HCV infection, linking infected patients to care, and curing HCV before patients begin to experience the consequences of cirrhosis and end-stage liver disease.

It is not clear, however, exactly who should be targeted for HCV testing. Similar to the conversation around HIV testing, there are several approaches to screening for HCV that may provide high yield and improve outcomes including: 1) targeted testing of the highest-risk groups, 2) routine testing among specific demographic groups that are readily identified and who have a high prevalence of HCV infection, and 3) routine testing throughout the entire population. This review develops a rubric by which to measure and characterize the HCV epidemic within a country, surveys the literature about the cost–effectiveness of screening for HCV in various populations, and discusses how epidemiology within a country should inform decision-making about who to test for HCV.
3. Overview of report
This report does not represent the results of a full systematic review. It is meant to serve as a summary of existing studies on cost–effectiveness of screening and treatment for HCV, with an analytic summary of key considerations. It was envisaged that there was a lack of relevant literature in low- and middle-income countries (LMICs), so existing studies from high-income countries (HICs) are described and their potential uses and limitations, when drawing conclusions are discussed.

4. Summary of global HCV epidemiology
Generally, HCV epidemics around the world are heterogeneous and represent mixtures of three core epidemic components:

4. Infection related to high-risk behaviours: In essentially every geographical region, the highest prevalence of HCV infection is among persons who use injection drugs (PWID).5,6 The prevalence of injection drug use differs between countries and regions, but within those who do inject drugs, HCV prevalence is nearly universally high. Commercial sex workers and prisoners also have increased prevalence (presumably related to both drug use and perhaps sexual transmission),7,8 as do men who have sex with men, especially those who are HIV infected.9 In many cohorts of PWID in North America, Europe, and Asia, HCV prevalence ranges from 30% to 75%.

5. Infection related to past generalized exposures that have since been identified and removed: This epidemic pattern, in which there is a high prevalence of HCV within a given age group, is commonly referred to as a “birth cohort epidemic”.10 While typically identified as being the infection pattern in North America and Europe, many nations have some element of birth cohort epidemics with their unique HCV epidemiology (Table 1).11 Birth cohort epidemics reflect an HCV exposure source that was once present and to which a large portion of the population was exposed, but that has since been identified and removed. For example, before it was identified and sequenced, HCV infected the blood supply of many countries in all regions of the world. When the blood supply began to be screened for the presence of HCV, the exposure was removed. As a result, the incidence of HCV fell dramatically among the general population, but there remains a burden of prevalent, chronic HCV among patients who were alive and likely to get a blood transfusion during the time that HCV existed in the blood supply.

6. Generalized population epidemic: This pattern is related to a widespread exposure, often iatrogenic, that results in high prevalence (8–10%) across essentially all age groups. Note that the primary difference between a “birth cohort” pattern and a generalized pattern of infection is the duration of time that the generalized exposure existed and whether it has been removed or mitigated. An example of a generalized exposure is the common use of reusable hypodermic syringes and needles in medical settings without adequate sterilization between uses.

Few epidemics fall into one of the above three categories. Rather, most are mixed, and represent some combination of all components (Table 1). The nature of an epidemic
within a specific country determines a great deal about the appropriate approaches to who to screen.

<table>
<thead>
<tr>
<th>Epidemic scenarios HCV</th>
<th>Definition</th>
<th>Disaggregation</th>
<th>Country example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalized</strong></td>
<td>High (&gt;5%)</td>
<td>With birth cohort</td>
<td>(N=23) Cameroon, CAR, Armenia, Egypt, Liberia, Gabon, Guinea, Ghana, Guinea-Bissau, Mongolia, Sierra Leone, Uzbekistan, Cape Verde, Chad, Mali, Niger, Nigeria, Pakistan, San Tome et Principe, Senegal, Togo, Burkina Faso, Georgia</td>
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<tr>
<td></td>
<td></td>
<td>Without birth cohort</td>
<td></td>
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<tr>
<td>High intermediate (3–5%)</td>
<td>With birth cohort</td>
<td>(N=14) Angola, Bahrain, Congo, Democratic Republic of the Congo, Equatorial Guinea, Estonia, Lebanon, Moldova, Russia, Taiwan, Turkmenistan, Ukraine, United Arab Emirates, Oman</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Without birth cohort</td>
<td></td>
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<tr>
<td>Low intermediate (2–3%)</td>
<td>With birth cohort</td>
<td>(N=44) American Samoa, Anguilla, Azerbaijan, Benin, Bermuda, British Virgin Isles, Cayman Islands, Cook Islands, Cote d'Ivoire, Falkland Islands, Faroe Islands, Gibraltar, Greenland, Holy See, Hong Kong, Iraq, Isle of Man, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Latvia, Liechtenstein, Lithuania, Macau, Monaco, Montserrat, Nauru, Niue, Northern Mariana, Islands, Palau, Palestine, Romania, St Helena, St Kitts and Nevis, St Pierre and Miquelon, San Marino, St Martin, Tajikistan, Thailand, Tokelau, Turks and Caicos, Tuvalu, Wallis and Futuna</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Without birth cohort</td>
<td></td>
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<tr>
<td><strong>Mixed</strong></td>
<td>Generalized population prevalence, low, moderate or high with a sizeable risk population (PWID)</td>
<td></td>
<td>(N=3) Pakistan, Egypt, Uzbekistan</td>
</tr>
<tr>
<td></td>
<td>High generalized</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High intermediate generalized</td>
<td></td>
<td>(N=5) Estonia, Kazakhstan, Taiwan, Turkmenistan, Ukraine</td>
</tr>
<tr>
<td></td>
<td>Low intermediate generalized</td>
<td></td>
<td>(N=8) Hong Kong, Latvia, Lithuania, Palestine, Romania, Thailand, Tajikistan, Syria</td>
</tr>
<tr>
<td></td>
<td>Low (1–2%) with PWID</td>
<td></td>
<td>(N=46) Albania, Algeria, Argentina, Australia, Belarus, Bhutan, Bosnia, Brazil, Cambodia, Chile, China, Colombia, Costa Rica, Croatia, El Salvador, Greece, Honduras, Israel, Italy, Japan, Kenya, Former Yugoslav Republic of Macedonia, Malaysia, Mauritius, Mexico, Montenegro, Morocco, Myanmar, Nepal, New Zealand, Nicaragua, Panama, Paraguay, Portugal, Puerto Rico, Serbia, Slovakia, Slovenia, South Sudan, Spain, Switzerland, United States, United States Virgin Islands, Uruguay, Viet Nam, Yemen</td>
</tr>
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5. Summary of the literature – Who to screen? What is the evidence base from modelling of the impact and cost-effectiveness of different screening approaches using different prevalence thresholds?

Testing in high-risk groups, including persons who inject drugs, MSM, prisoners, HIV-infected persons, and commercial sex workers

5.1. Persons who inject drugs

Multiple analyses in many geographical regions concur that routine testing for HCV in venues with a high prevalence of persons who inject drugs is cost-effective, even when the studies assume very poor follow-up rates and limited access to therapy. Further, dynamic HCV transmission models suggest that aggressive diagnosis and treatment among current drug users could reduce the incidence of HCV – “cure as prevention”. With typical prevalence estimates of 40%, but ranging as high as 75% in some cohorts, routine screening for HCV is almost certainly cost-effective. It is essential to consider the HCV cascade of care when screening recent or current drug users. Modelling studies demonstrate that even 100%
effective HCV therapy has almost no impact on population-level outcomes without efforts to
significantly improve the number of HCV-infected patients who initiate therapy.\textsuperscript{16}

5.2. Men who have sex with men

Men who have sex with men (MSM) are also at an increased risk of HCV incidence, particularly
if they are also HIV-positive. Since the mid-2000s, outbreaks have surfaced in the US, Europe
and Australia among HIV-positive MSM.\textsuperscript{17,18} Cost–effectiveness modelling has found testing
using liver function tests in combination with HCV Ab testing to be cost–effective in the HIV-
positive MSM population.\textsuperscript{19} Preliminary studies have suggested that core-antigen testing has
the potential to be cost–effective in this population as well.\textsuperscript{20} The results of these studies are
dependent on appropriate linkage to effective therapy and retention in care. These studies do
not fully account for either the reduction in secondary transmission or the possibility of
reinfection in high-risk groups.

5.3. Prisoners

Prisons likely have high HCV prevalence as the result of a high prevalence of persons who
inject drugs in prisons. One challenge to HCV testing in prisons is that new treatments for HCV
are costly and many prisoners do not have access to new therapies. A UK-based study,
however, found that HCV case detection, using dried blood spot testing, was cost–effective,
even when the model assumed low rates of HCV treatment initiation.\textsuperscript{21} A second study
concurs that screening in prisons can be cost–effective, but this study concluded that
targeting screening to those prisoners with a history of injection drug use improves cost–
effectiveness.\textsuperscript{22} A later study by several of the same authors found that routine screening of all
prisoners is not cost–effective, although that study found significant uncertainty in the results.
If the prison population had more advanced disease at the time of screening, or if the rate of
HCV disease progression is faster than estimated in the base case, then routine screening in
prisons can be cost–effective.\textsuperscript{23}

5.4. HIV-infected persons

Screening for incident and acute HCV in HIV-infected MSM is likely cost–effective.\textsuperscript{19} Although
nearly every guideline for HCV care recommends HCV screening at enrolment in care, we
were not able to find a cost-effectiveness analysis that answers the specific question of the
cost-effectiveness of HCV testing at enrollment in HCV care. Because the prevalence of HCV is
known to be high in HIV-infected persons, the pace of progression of fibrosis in HIV/HCV-
coinfected patients is high, and new therapies to treat HCV are effective in HIV/HCV coinfection, testing for HCV at enrolment in HCV is almost certainly cost–effective.

5.5. Sex workers

We were not able to find a study that addresses the cost–effectiveness of HCV testing in sex workers. Because many sex workers are also PWID or non-injection drug users, the prevalence of HCV in this group is likely high. It is not clear at this time, however, if it is cost–effective to routinely screen all sex workers, compared to an approach that targets testing to sex workers who report a history of injection drug use.

5.6. Testing among easily identified age or demographic groups known to have high HCV prevalence (“birth-cohort testing”)

Whenever there is an easily identified demographic group that has high HCV prevalence (for example, all individuals born in a certain time period) it is likely cost–effective to routinely test for HCV within that cohort. Several cost–effectiveness studies in the US estimate incremental cost–effectiveness ratios of “birth cohort” screening that are below commonly cited willingness to pay thresholds for resource-rich countries. Each of these studies compared “birth cohort testing” to the current standard of care, and shared the same qualitative conclusions. Similarly, one study from Portugal found that birth cohort testing was cost–effective in that country. Notably, based on Portugal’s local HCV epidemiology, the cohort to test is not identical to that in the US. Routine screening is preferred to targeted screening because providers are often not skilled at identifying high-risk behaviours, and because for many patients in such an epidemic, the “risk” to target is simply being a member of a high-prevalence age cohort (i.e. there are no specific behavioural risks to identify).

5.7. Testing among the general population without attempt to identify high-risk behaviours or characteristics (“routine testing”)

At this time, no jurisdiction of which we are aware recommends routine testing for all individuals regardless of demographics or specific behavioural risk. The data about population screening typically come from HICs such as the US and UK, and such studies find that routine testing in the general population is not cost–effective. For example, one cost–effectiveness analysis, conducted in the US context, found that when the general population prevalence of
HCV infection exceeded 0.53%, the incremental cost–effectiveness ratio of routine universal screening compared to targeted screening was far below commonly cited US willingness to pay thresholds. When compared to “birth cohort testing,” however, universal testing resulted in worse outcomes and higher costs than the birth cohort approach. This analysis raises the spectre that in countries whose HCV epidemic is largely concentrated to a specific birth cohort or demographics group, attempting to identify cases by routine testing of the entire population can dilute the testing effort and result in fewer cases of HCV being identified.

Similarly, a recent study in the US context investigated the cost–effectiveness of two approaches to testing for HCV in average-risk, asymptomatic adults accessing primary care: a) HCV EIA followed by quantitative RNA for those with positive EIA results, and b) quantitative RNA for all patients. Neither strategy was cost–effective.

An older study, conducted in the UK, also found that although screening high-risk groups in primary care settings was cost–effective, extending screening beyond high-risk individuals was not. Importantly, however, that study pre-dates the existence of effective, antiviral therapy targeting HCV. Higher efficacy of therapy could improve cost–effectiveness conclusions.

Similarly, a study conducted in Japan found that routine testing of the population was cost–effective compared to “no screening.” That paper, however, did not consider a birth cohort approach, and the conclusions therefore are not certain.

Another analysis, conducted in Italy, used Markov modelling to compare “testing” to “no testing” among patients who had undergone surgery. They found that testing was not cost–effective in this group. Notably, individuals who have undergone surgery are more likely to have had exposure to blood products, and therefore likely have a higher HCV prevalence then the general population. If screening among these patients was not cost–effective, screening in even lower prevalence groups, such as the general population, will also not be cost–effective.

There is one recent study, conducted in Canada, that found that one-time testing of patients outside the “birth cohort” of those aged 65 years or older would be cost–effective by Canadian standards. It is difficult from that manuscript to determine the epidemiological assumptions that led to this finding, which differs from most US-based studies. One assumption that could have influenced the results was that early-stage HCV had a low quality of life, which tends to make screening and treating HCV more cost–effective.

Similarly, a modelling study based on ten years of retrospective data at a London antenatal clinic found that routine testing for HCV for pregnant women was cost–effective, even at baseline prevalence levels as low as 0.1%. This contradicts the findings of a 2005 paper based in the US, which found that screening of asymptomatic pregnant women in the US, even when coupled with elective caesarean delivery to minimize antenatal transmission risk, was not cost–effective. It also contradicts a paper based in the Netherlands that found that adding routine one-time testing for HCV in antenatal clinics would not be cost–effective. These disparate findings may be influenced by estimates of fibrosis progression, discounting rates, and health-care costs in each country.
Importantly, all of the above studies reflect the epidemiology of HCV in HICs. One recent paper explicitly studied the cost–effectiveness in Egypt of one-time, routine screening for HCV followed by treatment with either pegylated interferon and ribavirin (PEG-RBV) or PEG-RBV plus an HCV protease inhibitor. Given the very high prevalence of disease, screening was always cost–effective, and often cost-saving. It is important to consider, however, that assumptions about linkage to HCV care and availability of treatment after diagnosis impact cost–effectiveness conclusions. If general population screening will likely identify many cases of HCV, but those who are infected have limited options for treatment, screening may not be cost–effective.

6. Drivers of cost–effectiveness

The main benefit of testing is identifying cases of HCV before they lead to the sequelae of end-stage liver disease; the resource implications of testing broadly are important. First, the cost of testing itself is not trivial. Second, if the testing strategy (i.e. the laboratory protocol one uses to identify HCV exposure and test for HCV viraemia) results in a large number of false-positive tests, the cost of unnecessary HCV therapy could be very large. At the same time, trying to “over target” testing to only the highest-risk groups can be detrimental to public health. Many high-risk behaviours are stigmatized and underreported, and health-care workers are not always skilled at identifying high-risk behaviours. Balancing these considerations is a challenge, and requires country-level determination of best approaches. General themes that should inform the screening approach include the following:

1. **HCV prevalence** — screening provides increasing value as prevalence rises. In one US based study, screening was cost–effective (compared to no screening) at a US willingness to pay threshold down to prevalence of 0.53%. Importantly, however, choice of comparator impacts the incremental cost–effectiveness ratio of routine population testing. When routine testing was compared to “birth cohort testing” in that same paper, routine screening diluted the screening effort in the cohort with the highest prevalence of HCV and therefore resulted in fewer cases of HCV identified and higher cost than “birth cohort testing.” However, in any population subgroup that has HCV prevalence >1%, it is likely that some form of testing is cost–effective. The question in such scenarios is whether to routinely screen, or to attempt to identify risk and target screening to that group.

2. **Degree of concentration of the epidemic** — to the extent that an epidemic is concentrated to a specific risk or demographic group, targeting screening to that group becomes more cost–effective. This dynamic is most directly at play when considering “birth cohort testing.” Being a member of a birth cohort is easily determined and generally carries no stigma. Thus, targeting testing to birth cohorts is feasible and often cost–effective. In countries with a strong birth cohort dynamic, birth cohort screening is likely preferred. To the extent that epidemics are concentrated among high-risk groups such as PWID, however, targeted testing is more challenging. Because HCV risk behaviours are stigmatized and underreported, trying to identify high-risk individuals is difficult and prone to under-testing high-risk patients.
3. **Treatment rates** – screening clearly becomes less cost–effective when identified patients cannot link to effective therapy. US-based analyses typically assume availability of interferon-free regimens to cure HCV. If such treatments are not available, or only available to a limited proportion of identified cases, then the incremental cost–effectiveness ratio of screening increases.

4. **Assumptions about the HCV cascade of care** – similar to treatment rates, loss to follow up has an important impact on cost–effectiveness conclusions. As the proportion of patients with identified HCV infection who successfully link to HCV care decreases, the incremental cost–effectiveness ratio of screening also goes up.

5. **Cost of testing** – the cost of testing may impact the cost–effectiveness of one testing strategy compared to another (i.e. which tests to use and in what order), but it has little impact on the cost–effectiveness conclusions about who to screen. In one study conducted in the US, ranging the cost of testing by as much as 50% in either direction had no impact on cost–effectiveness conclusions.\(^{37}\)

6. **Efficacy of HCV therapy** – the cost–effectiveness of HCV testing depends in part on the efficacy of HCV treatment. This dynamic is easily demonstrated by a hypothetical scenario, in which patients with identified HCV do not receive any therapy (efficacy = 0%). In such a case, the incremental benefit of screening would be zero, and the incremental cost–effectiveness ratio would approach infinity (no value).

7. **Cost of HCV therapy** – as the cost of treatment increases, the incremental cost–effectiveness ratio also increases. This is not surprising, as the cost of therapy has no impact on clinical outcomes (denominator of the cost–effectiveness ratio), but does increase cost (the numerator of the cost–effectiveness ratio). For example, in one US study, the incremental cost–effectiveness ratio of “birth cohort testing” compared to no testing increased more than 100% when one assumed treatment with pegylated interferon, ribavirin, and an HCV protease inhibitor compared to pegylated interferon and ribavirin alone.

8. **Estimates of quality of life with early-stage HCV** – if early-stage HCV has a large impact on quality of life, then testing (via any approach) becomes more cost–effective. If early-stage HCV has little impact on quality of life, then the benefits of testing accrue only to the minority of patients who become cirrhotic, and only in the distant future when those patients begin to experience complications of end-stage liver disease. In contrast, if early-stage HCV has an immediate impact on quality of life, then every patient with identified and cured HCV accrues lifetime benefits that greatly increase the benefits of testing.

9. **HCV fibrosis progression rates** – most of the sequelae of chronic HCV infection and essentially all HCV-attributable mortality, accrue only when a patient has reached cirrhosis. The time from HCV infection to development of cirrhosis is highly variable and can be as long as 25 years. Some patients never become cirrhotic. Faster rates of fibrosis progression tend to make testing for HCV more cost–effective, because faster fibrosis progression results in a larger proportion of the population experiencing sequelae of HCV.
7. What further research needs to be done to fill this information gap

It is important to collect accurate epidemiological data to better inform decision-making around HCV testing. A formal cost–effectiveness analysis that compares “targeted” vs “birth cohort” vs “routine” testing requires estimates of the prevalence of high-risk behaviours, stratified by age, the prevalence of HCV among those with high- and low-risk behaviours, stratified by age, and the age structure of the population. Further, it is important to know the cost of both HCV therapy in a country, as well as the costs associated with untreated HCV and end-stage liver disease. In addition, more implementation research in LMICs is needed to determine the degree to which providers can accurately identify and test high-risk patients when employing a targeted approach, as well as estimate of linkage to HCV care and the HCV cascade.

8. Conclusions – who should be tested for HCV?

- Testing in high-risk groups such as PWID, MSM, prisoners, HIV-infected persons, and commercial sex workers is likely cost–effective. Testing in settings with a high prevalence of high-risk patients is almost certainly cost–effective in all locations. It is important, however, to ensure adequate follow up after diagnosis.

- The best approach to testing outside of high-risk risk groups depends a great deal on a country’s unique HCV epidemiology. Most countries have at least some component of “birth cohort” epidemic, and “birth cohort” testing is likely cost–effective in most settings.

- Routine testing of the entire population carries two risks. First, when the HCV epidemic is concentrated to a specific age or risk group, generalized testing can dilute the testing effort and reduce the number of HCV cases identified. Second, if an epidemic is highly concentrated within a specific risk or demographic group, screening outside of that group can be inefficient and increase costs. Countries with high HCV prevalence across the entire population should implement routine screening, but in most epidemics, routine screening in the entire population may not be cost–effective. The specific threshold at which a country should alter its approach to routine testing, however, is a function of multiple factors and cannot be identified more generally.

References


