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Global hepatitis C elimination: an investment framework

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Keywords: hepatitis C; disease elimination; universal health coverage; cost-effectiveness; return on investment.

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1 **Summary**

2 The World Health Organization (WHO) has set global targets for the elimination of hepatitis B and
3 hepatitis C as a public health threat by 2030. However, investment in elimination programs remains
4 low. To drive political commitment and catalyse domestic and international financing, we developed
5 the first global investment framework for the elimination of hepatitis B and hepatitis C. This
6 manuscript focuses on the hepatitis C investment framework. The work was accompanied by
7 modelling demonstrating the cost of scaling up hepatitis C-specific elimination activities to meet
8 WHO's targets, considering both direct and indirect economic benefits. The investment framework
9 outlines national and international activities that will enable reductions in hepatitis C incidence and
10 mortality and identifies potential sources of funding and tools to help countries build the economic
11 case for investing in national elimination activities. The modelling demonstrated how strengthening
12 health systems, through improving workforce capacity and surveillance systems and integrating
13 activities into universal health programs, can improve coordination and optimize resource allocation,
14 making hepatitis C elimination cost-saving by 2027, with a net economic benefit of US\$22.7 (\$17.1-
15 27.9) billion by 2030. This is the first global investment framework for hepatitis C elimination; it
16 demonstrates a way forward for countries, particularly those with limited resources, to gain the
17 substantial economic benefit and cost savings that come from investing in hepatitis C elimination.

18

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23

24 **Search strategy and selection criteria**

25 References published between 2010 and May 1, 2019 were identified through searches of PubMed,
26 MEDLINE; EMBASE and grey literature, using the search terms "viral hepatitis", "hepatitis C",
27 "prevention", "testing", "treatment", "elimination", "financing", "economic modelling" and "cost-
28 effectiveness". In addition, we reviewed published case studies, reports and interviewed global
29 experts including epidemiologists, clinicians, community advocates, public health experts and
30 policymakers, to inform the framework and identify countries that have achieved viral elimination
31 targets. Only papers published in English were reviewed. The final reference list was generated on
32 the basis of originality and relevance to the broad scope of this review.

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Introduction

In 2016, the World Health Assembly adopted the WHO Global Health Sector Strategy (GHSS) on Viral Hepatitis 2016–2021,(1) which provided a roadmap for the elimination of hepatitis B and hepatitis C and outlined clear elimination targets, including an 80% reduction in new chronic infections and a 65% reduction in mortality compared to 2015 levels. While 194 countries have endorsed the strategy, far fewer have developed national plans for viral hepatitis elimination,(2) with a minority adopting a public health approach to eliminating viral hepatitis. In many countries the major barriers to a comprehensive response are leadership and political will, exacerbated by competing priorities and scarce resources,(1) particularly in high-endemicity areas.(3) A recent *Lancet Gastroenterology & Hepatology* Commission – focusing on ‘Accelerating the elimination of viral hepatitis’(3) – identified 20 heavily burdened countries that account for over 75% of the global burden of viral hepatitis and highlighted the need for these countries to mobilise domestic funding to address it. The Commission outlined innovative financing models to support country-level elimination programmes, and called for the development of an investment case for viral hepatitis to demonstrate the feasibility of elimination and quantify its health, social, and economic benefits.

With an estimated 71 million people living with the hepatitis C infection, at current rates hepatitis C will account for 0.84 million deaths annually by 2040 due to cirrhosis and liver cancer.(4) However, new treatments known as direct-acting antivirals (DAAs) have revolutionised hepatitis C care, with cure rates of over 95% following 8–12 weeks of once-daily well-tolerated tablets, providing a unique opportunity to eliminate hepatitis C as a global public health threat. Since DAAs became available in 2013,(5) they have been shown to reduce the risk of liver failure and liver cancer (6, 7) and improve patients’ quality of life.(8, 9) A full course of generic DAAs can now be purchased for less than US\$100 in multiple countries,(10) but are cost-effective even at a much higher cost across a range of

59 low, middle, and high-income country settings.(11, 12, 13) Nonetheless, globally, treatment
60 coverage remains low, with an estimated 1.5 million people initiating DAA-based treatment by 2016,
61 leaving the majority of people living with hepatitis C infection untreated.(14) Emerging data on the
62 productivity losses associated with hepatitis C, and conversely the improvements in productivity
63 post-cure (15-17), will help quantify the broader economic losses attributable to hepatitis C (18, 19).
64 A recent WHO costing exercise (20) estimated that a total cost of \$16.0 billion was needed for
65 hepatitis C testing and treatment costs, in addition to \$20.5 billion for programme costs to
66 implement the elimination of hepatitis by 2030 among 67 countries. Identifying sources of
67 investment and building the economic case for countries to invest in national hepatitis C-related
68 activities will be critical to achieving global elimination targets.

69

70 In 2011, to capitalise on strong political commitment, an investment approach for an effective
71 response to HIV/AIDS was published, and was seen as a major turning point in the HIV epidemic.(21)
72 It demonstrated how major efficiency gains could be realised through the rapid scale-up of HIV/AIDS
73 prevention, treatment, and care programs, by harnessing social mobilisation, increasing synergies
74 between programme elements, and promoting the benefits of treatment as prevention. A
75 comparable, strategic approach to investment in prevention, testing and treatment activities for
76 hepatitis B and hepatitis C elimination is needed.

77

78 *A global investment framework for viral hepatitis elimination*

79 Building on the work of the WHO GHSS on viral hepatitis (2016),(1) we developed a strategic
80 investment framework (**Figure 1**) for the global elimination of hepatitis B and hepatitis C by 2030.
81 While these diseases have different epidemic characteristics, they share many similarities in health
82 system requirements and approaches for effective disease control,(3) including interventions to
83 prevent infections (safety of blood supply, safety of health care-associated injections) and testing

84 and treatment programmes that are delivered through common platforms (population-based,
85 community-level, health centre, primary, secondary, tertiary-level hospitals) and workforces
86 (specialists, doctors and nurses).(22) The framework adopts a public health and health systems
87 strengthening approach to identify national and international activities that would support country-
88 level implementation of viral hepatitis elimination strategies across diverse settings. For the
89 purposes of this paper, we focus on hepatitis C elimination to demonstrate how policymakers and
90 others can use this framework to support and justify investment in hepatitis C activities.

91

92 *An investment framework for hepatitis C elimination*

93 Firstly, the framework identifies the importance of using multiple financing mechanisms to
94 encourage investment from domestic, private sector and international sources and enable
95 policymakers and financiers to galvanise support for action. Secondly, the framework identifies
96 activities that countries and international agencies can implement, along with critical enablers to
97 allow the effective implementation of hepatitis C programmes at scale. Finally, the framework
98 outlines the economic benefits of achieving hepatitis C elimination, including direct, indirect and
99 cross-sectoral economic benefits, and the broader benefits that investment can provide through
100 health systems strengthening. To demonstrate the impact of the investment framework, we
101 modelled two investment scenarios for hepatitis C: *elimination* – where investments in activities
102 were scaled up to meet the WHO 2030 diagnosis and treatment elimination targets, and *progress* –
103 where more modest investments in activities were made to implement current WHO screening
104 guidelines. The models estimate the impact, cost, cost-effectiveness and economic benefits over
105 time of both scenarios at a global and WHO regional level. Uniquely, the models estimate the
106 economic productivity losses associated with hepatitis C infection due to absenteeism and
107 presenteeism. A detailed model description and additional findings are explored in the
108 accompanying modelling paper.(23)

109 **Financing hepatitis C elimination activities**

110 Hepatitis C elimination will require considerable leadership, political will, and financial investment.
111 Global financing mechanisms, such as the Global Fund,(24) Gavi,(25) and Unitaid,(26) have
112 successfully brought together elements of the financing value chain to mobilise, pool and invest in or
113 “replenish” health programmes.(27) As of July 2018, the Global Fund had disbursed more than
114 \$38 billion (24) for HIV/AIDS, tuberculosis, malaria, and health systems. However, its recent global
115 strategy 2017–2022 did not mention hepatitis C.(28) More directly, Unitaid (26) has invested \$60
116 million since 2013 in programmes that aim to develop better, simpler, point-of-care diagnostic tools
117 and support countries to negotiate gain access to cheap hepatitis C medicines, and integrate
118 hepatitis C testing and treatment into HIV programmes.(29) However, in the current context of
119 shrinking aid budgets and reduced development assistance for health,(30) significant new funding to
120 support a global response to hepatitis C elimination is unlikely. For most countries, funding for
121 hepatitis C programmes will be reliant on domestic and innovative financing sources and blended
122 finance instruments to sustain and scale up health programmes.(27) Domestic sources already
123 account for most of the funding for the development of country-level responses to hepatitis C,(3)
124 highlighting the need for clear strategies to enable countries to support intervention scale-up and
125 delineate stakeholder responsibility, accountability, and funding models.

126

127 In 2016, a report (31) on innovative financing of hepatitis B and hepatitis C prevention and
128 treatment in low and middle-income countries (LMICs) outlined how a combination of funding
129 mechanisms, adapted to the context of the country, payers and patients, will be needed to
130 accurately target country-specific challenges. It promoted public-private partnerships with a focus
131 on non-infrastructure interventions and a shared value approach to enable countries to partner
132 with pharmaceutical and diagnostic companies where there are clear synergies between public
133 health programmes and companies’ commercial activities. In 2018, the United Nations Secretary-

134 General launched the Strategy for Financing the 2030 Agenda for Sustainable Development,(32)
135 which identified actions to support countries to accelerate financing the Sustainable Development
136 Goals (SDGs), including aligning global economic policies and financial systems with the 2030
137 Agenda; enhancing sustainable financing strategies and investments at the regional and country
138 levels; and seizing the potential of financial innovations, new technologies and digitisation to provide
139 inclusive and more equitable access to finance.

140

141 Positioning national hepatitis C responses within a framework of universal health care (UHC) and the
142 broader SDGs (1) can enable policymakers to leverage the roll-out of UHC for investment in hepatitis
143 C programmes while facilitating prevention, diagnosis and early management of other major health
144 conditions, including liver cancer, hepatitis B, HIV, tuberculosis, and other chronic diseases such as
145 diabetes and hypertension.(33) Many of the strategies and infrastructure required for hepatitis C
146 elimination can be effectively added to existing HIV (and potentially tuberculosis and other UHC)
147 programmes at little additional cost,(34) with examples of this currently underway in Georgia (35),
148 Rwanda (36), and Ukraine (37). Multiple policy and economic mechanisms can be utilised to improve
149 the affordability of hepatitis C elimination. **Table 1** summarises theses and describes how these
150 mechanisms have been utilised to finance various health-related issues, with reference to countries
151 where these approaches have been implemented successfully.

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156 **Key elimination activities**

157 Our investment framework identifies *national* and *international* activities that would support the
158 elimination of hepatitis C, along with critical enablers to allow hepatitis C programmes to be

159 implemented effectively at scale (**Table 2**). These were framed to address existing challenges that
160 underpin the lack of investment and action in many countries, which are often interlinked and have
161 cascading impacts that perpetuate each other in a negatively reinforced cycle (**Figure 2**). For
162 example, many LMICs with a growing hepatitis C disease burden lack a formally costed hepatitis C
163 elimination programme. This can arise from a lack of awareness among policymakers about the
164 burden of hepatitis C-related disease and potential benefits of prioritization of hepatitis C
165 elimination. This lack of awareness of the disease burden is often driven by inadequate data and
166 weak surveillance systems. These in turn reduce governments' capacity to prioritize resource
167 allocation for national viral hepatitis elimination action plans and limited public sector-optimized
168 procurement of medicines or diagnostics. Countries then have fragmented procurement, rather than
169 national pooled procurement; this can lead to a high mark-up in drug prices from pharmaceutical
170 companies, and the perception that DAAs are expensive. This in turn prevents national programme
171 managers from investing and consequently they miss valuable opportunities to appropriately invest
172 in hepatitis C elimination and maximise the return on investment.

173 **Table 2** details the national and international activities and *key enablers* of hepatitis C elimination,
174 tools to support the implementation of these activities, and countries that are successfully
175 implementing activities. *National activities* include purchased commodities and programmes that
176 have a direct effect on reducing hepatitis C transmission, morbidity, and mortality. These should be
177 informed by surveillance data and local epidemiology and scaled up according to the size of the
178 affected population. Supporting governments to develop national plans and local investment case
179 will help to raise the profile of hepatitis C elimination and build political commitment through global,
180 regional, national and local forums to catalyse action and financing. Strengthening and integrating
181 viral hepatitis surveillance and monitoring systems within national information systems can aid
182 national and local governments assess the nature of the epidemic, the true burden of disease and
183 attributable cost to the country. This enables improvement of resource allocation for services and

184 workforce training. A roadmap for such an approach can be found in the WHO viral hepatitis C
185 continuum of care monitoring and evaluation framework.(38) In many settings, the effectiveness of
186 viral hepatitis programmes is limited by poor health infrastructure, including low laboratory capacity
187 and a lack of reliable supply chains for vaccines, medicines and diagnostics.(39) Investing in health
188 systems strengthening approaches that deliver public programmes that address multiple diseases,
189 with emphasis on task-shifting and task-sharing,(40, 41) will increase cost-efficiency and ensure
190 sustainability.(20) Promoting standardisation, simplification and decentralisation of health services
191 to reach and actively involve those populations most affected will help drive demand and ensure
192 population coverage. Supporting community sector advocacy and civil society engagement to
193 highlight inadequate hepatitis C funding and demand access to testing and treatment will help
194 support all *National activities* for HCV elimination.

195

196 Despite major reductions in the cost of hepatitis C treatments over the past few years,(10, 42) the
197 high costs of treatment and diagnostics mean that many countries cannot support the scale-up of
198 testing and treatment programmes needed to achieve elimination. Countries should explore Trade
199 Related Aspects of Intellectual Property Rights (TRIPS) flexibilities and licensing agreements and be
200 encouraged to employ voluntary licenses that allow production and supply of generic antiviral
201 medicines, currently available to 112 LMICs (home to 65.4% of the people living with hepatitis
202 C).(43) Licensees of the Medicines Patent Pool and Gilead may sell outside the 112 countries if no
203 granted patent is being infringed. This includes cases in which a compulsory licence is issued (44) by
204 a government authority to make use of a patent during the patent term without the authorization of
205 the patent holder to address a public health need. For example, compulsory licenses can allow local
206 production or importation of generic products (31) from other countries for the domestic market
207 without the consent of the patent holder, and against royalty payments; however, this has only been
208 used twice for hepatitis products.(45) Direct negotiations with pharmaceutical and diagnostic

209 companies has enabled reduced prices in Australia,(46) and Egypt (47, 48) and others. Ensuring
210 hepatitis C medicines and diagnostics are included in the national Essential Medicines List (EML),(49)
211 and Essential In Vitro Diagnostics List,(50) will be critical as many countries continue to expand their
212 UHC packages.

213

214 *International activities* are implemented by development and related agencies that impact on global
215 policy engagement and are designed to create the necessary environment for countries to achieve
216 elimination and encourage financial investment. Helping countries to identify and support priority
217 activities promotes prioritisation of activities based on an understanding of the in-country
218 epidemiology and context. This will be important because local technical expertise and capacity may
219 be lacking. Georgia’s technical advisory group, composed of local and international hepatitis C
220 experts to enable country ownership, has adopted a multi-stakeholder participatory approach to
221 develop strategies, objectives, and actions to help Georgia eliminate hepatitis C.(35, 51) Promoting
222 simplified clinical pathways and models of care that are integrated across related diseases and
223 platforms, including HIV, tuberculosis, and viral hepatitis, will help to reduce overall costs of
224 programmes and increase programme coverage.

225

226 *Key enablers* can facilitate the rapid scale-up of national hepatitis elimination activities and can be
227 classified into three categories. *Social enablers* make environments conducive to supporting the
228 uptake of hepatitis C elimination activities. For example, harnessing opportunities for publicity
229 through World Hepatitis Day, conferences, and other high-level meetings to increase the profile of
230 viral hepatitis elimination and advocating directly to government to reprioritize budgets to scale up
231 hepatitis C activities. *Policy enablers* support the scale-up of hepatitis activities and investment
232 approaches by providing a regulatory environment (laws, policies, and guidelines) to attract
233 investment, strengthen coordination with other health programmes, and identify opportunities for

234 health systems strengthening and cost-savings. For example, the integration of hepatitis C activities
235 into UHC country packages enables hepatitis C drugs to be listed on the national Essential Medicines
236 List and supports pooled procurement. *Program enablers* can enhance quality, coverage, and impact
237 of hepatitis C elimination activities through a public health approach,(39, 43) for example, ensuring
238 clinical testing and treatment guidelines and legislation can support universal access to hepatitis C
239 testing and treatment.

240 **The return on investment**

241 Beyond life-threatening complications, individuals infected with hepatitis C experience a reduction in
242 quality of life, decreased health and wellbeing, and substantial social stigma.(73) This can reduce
243 workforce participation and personal financial security,(17) and lead to direct costs to health
244 systems. Most of these healthcare costs typically occur 10–20 years after initial infection with the
245 onset of cirrhosis and liver cancer, which can be very costly and challenging to manage.(95) To gain
246 support and traction from financiers, a strong investment case is essential for country elimination
247 programmes. Epidemic and economic models have been used to support investment cases by
248 quantifying the impact, resource requirements, and return on investment of changes in viral
249 hepatitis disease control strategies.(69, 58, 96) However, much of the current work on viral hepatitis
250 elimination explores the cost-effectiveness of scaling up hepatitis C treatment by only taking into
251 account direct costs. Many of these analyses underestimate the current cost of chronic viral
252 hepatitis to the community because they do not consider decreased workforce participation and/or
253 reduced quality of life among people living with hepatitis.(15-17) Analyses that do not include
254 indirect economic productivity losses (15-19) fail to capture the longer-term economic benefits of
255 increased workforce participation among people who are cured and will not suffer premature death
256 and those who never become infected in the first place. Advancements in diagnostics and the
257 discovery of a cure for hepatitis C mean that major gains are now possible over short time horizons,
258 provided investment can be catalysed.

259

260 To demonstrate the utility of the Investment Framework, we produced model-based epidemic and
261 economic projections to assess the impact of two investment strategies for hepatitis C: an
262 “elimination strategy” and a “progress strategy”. In the elimination strategy, efforts were scaled up
263 to meet the WHO 2030 elimination targets of having 90% of people with hepatitis C diagnosed and
264 80% of diagnosed patients on treatment by 2030. In the progress strategy, a more modest

265 investment in hepatitis C testing and treatment was modelled to assess cost-effectiveness of
266 increased investments in hepatitis C without achieving elimination targets. The status quo and the
267 two investment scenarios were assessed for each of the WHO's six world regions; a detailed model
268 description and additional findings are explored in the accompanying modelling paper.(23)

269

270 Epidemiological impact of investment in hepatitis C

271 Based on current estimates of total people living with hepatitis C across the six WHO regions, the
272 application of the elimination strategy would substantially reduce the overall number of people
273 living with hepatitis C. The model projected that if hepatitis C testing and treatment were scaled up
274 according to the elimination scenario, an 85% (95% Credible Interval (CI) 70–92%) reduction in
275 annual hepatitis C incidence and a 47% (95% CI 27–63%) reduction in annual hepatitis C-related
276 mortality could be achieved by 2030, relative to 2015.

277 Compared to the status quo, this was estimated to prevent a cumulative 2.1 (95%CI 1.3–3.2) million
278 hepatitis C-related deaths and 10 (95%CI 4–14) million new hepatitis C infections globally between
279 2018-2030, and to substantially reduce the overall number of people living with hepatitis C. In the
280 progress scenario, minimal impact was made on incidence. This was due to the high prevalence
281 among risk populations, which meant that reinfection rates were high enough to negate the benefits
282 of treatment among populations such as people who inject drugs. In the status quo, progress and
283 elimination scenarios, 6%, 57% and 70% (respectively) of the global adult population were tested by
284 2030.

285

286 Economic impact of investment in hepatitis C

287 The cumulative cost of the elimination scenario was \$41.5 billion (\$33.1–48.7 billion) between 2018
288 and 2030 (\$23.4 billion more than the status-quo), with a peak in annual investment of \$4.8 billion
289 (\$3.2–5.7 billion) globally in 2019. By 2025, both the progress and elimination scenarios had

290 incremental cost-effectiveness ratios of under \$2,000 per disability-adjusted life year (DALY)
291 averted, reducing to \$842 (\$514–1,613) and \$885 (\$654–1,189) per DALY averted respectively by
292 2030. This does not include indirect economic benefits. The indirect economic benefits from scaling
293 up hepatitis C programmes continued to grow over time as a result of the cumulative morbidity and
294 mortality averted, leading to a larger and more productive workforce. The elimination scenario
295 produced a cumulative economic productivity gain of \$46.1 billion (\$35.9–53.8 billion) between
296 2018 and 2030 (by reducing cumulative productivity losses from \$273.8 billion in the status quo
297 scenario to \$227.7 billion). When the cumulative \$46.1 billion in productivity gains from elimination
298 were considered alongside the additional \$23.4 billion investment required compared to the status
299 quo scenario, hepatitis C elimination was estimated to become cost-saving by 2027 and lead to a net
300 global economic benefit of \$22.7 billion (\$17.1–27.9 billion) by 2030.(23)

301

302 *Cross-sectoral economic benefits of hepatitis C elimination and synergies with other development*
303 *sectors*

304 Achieving the SDG target for UHC requires global investment in infrastructure, and many countries
305 have already commenced major investments in health.(97) Integrating hepatitis C services within
306 these investment approaches and systems can significantly reduce costs compared to implementing
307 disease-specific programmes. The simplicity and safety of hepatitis C treatment means that most
308 services can be delivered through the primary care sector in many countries, making integration
309 highly achievable, and a recent costing study estimated that adding viral hepatitis elimination
310 activities (B and C) to UHC would only increase the total costs of UHC by 1.5%.(20) This is an
311 important consideration, because the human resource costs associated with testing, treatment and
312 cure can be more than double the commodity costs in many settings, and adequate human
313 resources may already exist and be financed in current health systems.(20) When the model
314 projections were re-run without additional human resource costs, the investment to eliminate

315 hepatitis C became cost-saving almost immediately (2019), compared to 2027 with 50% of staff costs
316 or 2030 with 100% of staff costs included. Procuring drugs at generic pricings was critical, with
317 elimination estimated to take until 2030 or 2037 to become cost-saving if drugs were \$1,000 or
318 \$5,000 respectively in high-income countries. This highlights the importance of continued global
319 efforts to universally reduce drug costs.(23).

320

321

322 **Discussion**

323 Eliminating the public health threat of hepatitis C is technically achievable. The challenge to
324 eliminate hepatitis C as a public health threat by 2030 is not that the targets are too ambitious to be
325 achieved, but that most countries globally are not investing sufficient funds and political effort to
326 achieve these targets. This investment framework provides a clear pathway for achieving the
327 financing mechanisms and activities required to reach viral hepatitis elimination and highlights the
328 substantial long-term health and financial benefits of meeting the 2030 elimination targets.
329 Countries should identify their specific challenges as highlighted in Figure 3, and – using this
330 investment framework and the accompanying modelling paper (23) – can begin to build political
331 commitment with the development of a national hepatitis plan that includes an investment case for
332 hepatitis C elimination. While it may not be realistic for all LMICs with high hepatitis C prevalence to
333 mobilise significant amounts of domestic funding in the short term, there are cost-neutral and low-
334 cost strategies that can build momentum and support for elimination (**Figure 3**). For countries with
335 lower hepatitis C prevalence and limited funding for hepatitis C treatment programmes, the
336 productivity gains and cost savings demonstrated in our models will be less. However these
337 countries can make considerable advances in hepatitis C elimination, at low cost, by adopting
338 synergistic and cost-sharing strategies such as the integration of hepatitis C services into existing
339 health programmes, such as HIV and tuberculosis programmes, which have existing infrastructure,
340 including skilled workforce and robust surveillance systems.

341

342 All countries, regardless of hepatitis C prevalence and burden, can leverage the expansion of UHC to
343 ensure hepatitis C services (testing and treatment) are included in their minimum package of health
344 services, which will substantially reduce costs.(20) Our models demonstrated that \$41.5 billion is
345 required between 2018 and 2030 to achieve global elimination, but that this is likely to be recovered
346 in cost savings by 2027, beyond which considerable additional economic returns are possible.
347 Rapidly reducing new infections and death from hepatitis C will also have a profound benefit on
348 future disease burden, (98) while generating major savings in healthcare costs associated with
349 managing severe liver disease and other health-related consequences of viral hepatitis. Unlike in
350 other diseases, highly effective treatments that cure hepatitis C disease enable the prevention of
351 deaths and new infections without ongoing costs as indicated in **Figure 3**. Moreover, early
352 investment can lead to substantially greater long-term economic benefits,(43, 57, 69) and as the
353 costs of diagnostics and treatment decline through advocacy, international support, private
354 partnerships and community mobilization, these benefits will increase.(10)

355

356 Most countries will need to increase their domestic financing and create fiscal space to invest in
357 hepatitis elimination programmes. As such, greater emphasis will need to be placed on the
358 economic benefits of hepatitis programmes, as outlined in this paper. Investment plans to support
359 national policies are needed to ensure evidence-informed decision-making regarding which
360 interventions will provide the greatest public health returns. If domestic efforts to provide funding
361 are unsuccessful, new streams of finance – including innovative financing mechanisms – to support
362 national programmes should be explored (see **Figure 1**).

363

364 While this paper presents an investment framework for global hepatitis C elimination, similar global
365 economic modelling has been demonstrated for hepatitis B (99) that identified how scaling up

366 coverage vaccination (to 90% of infants), birth-dose vaccination (to 80% of neonates), use of
367 peripartum antivirals (to 80% of hepatitis B e antigen-positive mothers), and population-wide testing
368 and treatment (to 80% of eligible people) could achieve hepatitis B elimination by 2030. Similarly,
369 positioning hepatitis B elimination activities within countries' UHC packages will help to ensure
370 sustainable funding for vaccines, diagnostics and medicines. China was an early adopter of a health
371 system strengthening approach to rapidly scale up hepatitis B immunisation to reach population
372 coverage.(100) The country negotiated local manufacturing for treatments and vaccines that have
373 significantly reduced prices and guaranteed supply while generating a new revenue stream. Such
374 investments have also stimulated national drug and vaccine production, ensuring sustainability of
375 the programme and the development of new in-country industries and technology markets.

376

377 **Conclusion**

378 Any elimination activity requires resourcing and significant investment at a country level, as
379 identified in the GHSS strategy on viral hepatitis. Identifying sources of investment and building the
380 economic case for countries to invest in national hepatitis C-related activities will be critical to
381 achieving global elimination targets. The investment framework presented herein outlines national
382 and international activities that will enable reductions in hepatitis C incidence and mortality and
383 identifies potential sources of funding and tools to help countries build the economic case for
384 investing in national elimination activities. This is the first global investment framework that has
385 demonstrated a substantial economic benefit of investing in hepatitis C elimination and
386 demonstrates how such investments would become cost-saving by 2027. Leveraging global support
387 and political will for the expansion of UHC, and ensuring hepatitis services are integrated into these
388 substantial new investments, will enable new funding sources for viral hepatitis elimination activities
389 as well as health systems' strengthening opportunities. Encouragingly, in September 2019 the United
390 National General Assembly included viral hepatitis in its political declaration on universal healthcare

391 demonstrating commitment by heads of state, political and health leaders and policymakers globally
392 to begin integrating hepatitis B and hepatitis C elimination programmes into UHC country
393 programmes. (101) Countries should utilise the investment case and existing evidence to raise the
394 profile of viral hepatitis elimination and build political commitment through global, regional, national
395 and local forums that engage affected communities, healthcare professionals and other key
396 stakeholders.
397

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Table 1. Mechanisms to improve financing for HCV elimination activities		
Financing Mechanisms	Approaches to support HCV elimination	Examples
Government health expenditure	<p>Increase overall Government health expenditure and increased budget allocation for Hepatitis C activities</p> <p>Development of HCV national plan & investment case to estimate size of the population living hepatitis C and overall costs to the community and government</p>	<p>Australia (46), Egypt (47-48), Scotland (58)</p> <p>African Union (31) countries committed to allocate at least 15% of their annual budget to improve the health sector in their country.</p>
Health insurance and Universal Health Coverage	<p>Increase access and use by making health services more affordable, through voluntary or mandatory health insurance and universal health coverage schemes</p>	Thailand (66), South Africa (64)
Influencing market forces to reduce costs of commodities	<p>Effective price negotiations with pharmaceutical manufacturers for hepatitis treatment and diagnostics</p> <p>Local Production of generics</p> <p>Volume or tiered pricing</p> <p>Medicines patent pool</p> <p>Compulsory licences / Patent challenges</p>	<p>Australia (46), Mercosur countries (94), Pakistan (71), India (44), Malaysia (90, 91)</p> <p>Affordable Medicines Facility – malaria (AMFm) (63), a pilot project funded by UNITAID and hosted by the Global Fund that negotiates price reductions of malaria treatments with manufacturers and provides a subsidy to buyers, through a co-payment.</p> <p>Argentina, Brazil, China, Morocco, the Russian Federation, Ukraine and Médecins du Monde are currently challenging the patent applications for sofosbuvir (31).</p>
Maximising effectiveness of public health spending	<p>Synergistic action creates opportunities to finance substantial improvements in HCV care without further straining health sector budgets via integration of viral hepatitis into existing services and UHC</p> <p>Adopting an investment case approach to guide investments for maximum impact</p> <p>Reallocation of existing funds towards hepatitis</p>	<p>South Africa (64, 65), Scotland (58)</p> <p>Debt2Health initiative (67)- initiative of the Global Fund that helps channel the resources of developing countries away from debt repayment and toward life-saving investments in health.</p>
Innovations and efficiencies over time	<p>Dried blood sampling to reduce diagnostics costs</p> <p>Non-specialist care, including task sharing and task-shifting</p> <p>Financial Transaction Tax</p>	<p>Australia (57), Scotland (58)</p> <p>UNITAID (27) has raised US\$2 billion from a €1 levy on air tickets leaving France. This ‘air levy’ now been applied in 15 countries globally.</p>
Private-Public Partnerships (PPP)	<p>Formal risk management mechanism – where public authorities partner with the private sector to provide services. PPP’s aims to share the risks and costs of investment, while enhancing the development of innovation through partnerships.</p>	<p>The Gavi Matching Fund (25) is a public-private funding mechanism designed to incentivise private sector investments in immunisation.</p> <p>RED (28, 67)- is a brand created to engage business and consumer power in the fight against AIDS in Africa. Branded products and services when purchased, activate corporate giving to the Global Fund. RED</p>

		has generated over US\$600 million in funds.
International donors'– development assistance for health	Provision of effective treatment through development assistance for health Low-cost diagnostics	UNITAID (29) is partnering with FIND to support the development of better, simpler, point-of-care diagnostic tools for HCV and introduce HCV testing and treatment into HIV programs in seven countries.
Sharing costs with other strategies	Harm reduction costs Immunisation and blood safety Coinfection with HIV and service delivery	Portugal (76), Pakistan, Rwanda (36), Brazil (61), Georgia (35) Pan American Health Organization (PAHO) Revolving Fund for vaccines (31) - for 35 years, the Revolving Fund of PAHO has helped Member States, pool their national resources to procure high-quality life-saving vaccines and related products at the lowest price.
Dedicated hepatitis fund	Create a global viral hepatitis fund to leverage resources and cultivate synergies through innovative public–private partnerships, and catalyse action on viral hepatitis. The proposed fund would primarily support the most-affected countries and communities where, despite national commitment, national health systems cannot adequately or effectively address hepatitis epidemics.	EndHEP2030 Fund (31) - is the only grant-making organization dedicated exclusively to the mission of ending viral hepatitis
Pooled financing	Bringing together development and commercial actors to pool financing and offer opportunities to scale up blended finance models	Global Procurement Fund (GPRO) (31) - works with participating countries to pool orders from member countries and uses international competitive bidding to purchase products at negotiated prices. GPRO only works with manufacturers that have freedom to operate – either with a license from the originator-companies or those with a license from the Medicines Patent Pool.
Results-based financing	Seeks to create market incentives to achieve critical social outcomes by only paying when results are achieved. Two main types: Performance-based financing targets the supply side, whereas conditional cash transfers target the demand side of a given market.	Since 2014, the Global Fund has implemented a Results Based Financing model in Rwanda (36), called 'National Strategy Financing' to incentivize results and efficiency.
Social Impact Bonds (SIB) and Development Impact Bonds (DIBs)	SIBs and DIBs draw on elements of impact investing and public-private partnerships and allow outcome funders to pay directly for the achievement of outcomes rather than for inputs. Investors provide the upfront risk capital and play a critical role in helping improve service delivery by bringing private sector discipline into practice.	Global Fund (25) supports a social impact bond to address HIV in adolescent girls and young women in South Africa. The International Finance Facility for Immunization uses donor pledges to issue vaccine bonds to raise money for Gavi Alliance.

Table 2. Challenges and activities to support investment in hepatitis C elimination, including tools and example countries

Challenges to hepatitis C elimination	Activities to support investment in <i>hepatitis C elimination</i>	Tools	Country Examples
<p>Weak surveillance systems and inadequate data</p> <ul style="list-style-type: none"> • Low-quality surveillance systems and a lack of reliable cause-specific mortality data for liver cancer and liver failure.(33) • A lack of quality data means the true economic impact of viral hepatitis – including healthcare costs, reduced quality of life, workforce participation and productivity – is substantially underestimated.(34, 35) • As a consequence, insufficient resources are allocated to the issue.(63) 	<p>National – Strengthen surveillance systems and monitor progress towards viral hepatitis elimination:</p> <ul style="list-style-type: none"> • Integrate hepatitis C indicators into national health information systems to assess hepatitis burden • Develop national plan and investment case • Monitor hepatitis C service access, uptake, and quality 	<ul style="list-style-type: none"> • WHO hepatitis C continuum of care monitoring and evaluation framework (38) 	<p>Australia (55-57) Georgia (35, 51) Scotland (58) Rwanda (36, 59)</p>
	<p>International – Set and monitor global targets to encourage countries to strengthen in-country surveillance systems:</p> <ul style="list-style-type: none"> • Advocate for the inclusion of hepatitis indicators into existing surveillance systems – e.g. HIV surveillance systems • Provide technical assistance to develop national plan and national targets • Provide country support for the development of investment case and financial investment monitoring • Provide country support for health information systems strengthening using strategic information tools 	<ul style="list-style-type: none"> • WHO – Country Health statistics and information systems (60) 	<p>Rwanda (36) Brazil (61)</p>
<p>A lack of awareness among policymakers & limited political will to prioritise hepatitis C elimination</p> <ul style="list-style-type: none"> • Often driven by inadequate data and weak surveillance systems,(2) competing health priorities, and limited health budgets.(1) • Compounded by a lack of awareness in the 	<p>National – Develop a national viral hepatitis elimination plan and local investment case:</p> <ul style="list-style-type: none"> • Mobilise political commitment • Identify key actors to optimise resource allocation & financing mechanisms • Develop country-specific targets and monitoring activities • Ensure supportive laws, policies and guidelines 	<ul style="list-style-type: none"> • World Hepatitis Day events and campaigns • Policy reports and briefing meetings with policymakers • National meetings, conferences, and other high-level political forums 	<p>Scotland (58) Australia (46) Egypt (48, 62)</p>

<p>general population and at-risk communities, who consequently fail to demand action from their governments (63)</p>	<p>International – Develop a global investment case:</p> <ul style="list-style-type: none"> • Raise the profile of hepatitis C elimination among policymakers and financiers • Garner political support, e.g. by demonstrating the economic benefits of viral hepatitis elimination • Attract global donor investments through evidence-based advocacy 	<ul style="list-style-type: none"> • Let's end hepC policy dashboard¹ 	<p>South Africa (64, 65) Rwanda (36, 59) Thailand (66)</p>
<p>Limited funding, donor support and investment in hepatitis C elimination activities</p> <ul style="list-style-type: none"> • Limited funding from global donors such as the Global Fund (67) and the Bill & Melinda Gates Foundation.(68) • Countries need to generate domestic revenue for elimination activities 	<p>National – Investment and financing for sustainability:</p> <ul style="list-style-type: none"> • Demonstrate cost-effectiveness (11, 69) and health benefits (56, 57) of hepatitis C elimination • Mobilise domestic resources by leveraging private investment and innovative financing models (31) • Advocate for inclusion of viral hepatitis activities in UHC packages and broader health financing approaches. • Support research and innovation towards optimised hepatitis C service delivery and elimination activities.(27) 	<ul style="list-style-type: none"> • Optima hepatitis C² • Cost-effectiveness calculator³ • National Viral Hepatitis Programme Financing Strategy Template⁴ 	<p>Brazil (61) Rwanda (36) Pakistan (70, 71)</p>
	<p>International – Develop international guidelines and tools to identify and support priority activities and stimulate investment:</p> <ul style="list-style-type: none"> • Support cost-effectiveness evaluations for hepatitis C programme activities • Identify and provide funding for priority activities • Facilitate investment in research and innovation • Promote innovative financing models to generate government revenue, attract private investment, and secure donor funds for priority activities 	<ul style="list-style-type: none"> • Optima hepatitis C² • Cost-effectiveness calculator³ • Cost-effectiveness analysis registry database⁵ 	<p>South Africa (64) Thailand (66)</p>

¹ Instituto de Ciências da Saúde, Portugal, with support from Gilead Sciences Europe, has developed a policy calculator for Portugal that is now being expanded to five European countries (Bulgaria, England, Germany, Romania and Spain). www.letsendhepc.com

² The Burnet Institute developed this tool to help decision-makers understand what it will take to reach targets and choose the best public health investments with current resources for their local setting. (www.ocds.co/hcv)

³ Harvard Medical School, with support from WHO and UNITAID, has developed a Hep C Calculator that allows the adaption of cost-effectiveness models to country-specific epidemics. (<http://tool.hepcccalculator.org/>)

⁴ World Hepatitis Alliance, National Viral Hepatitis Programme Financing Strategy Template. (<https://www.hepatitisfinance.org/investment-case/>)

⁵ Center for the Evaluation of Value and Risk in Health analyses the benefits, risks and costs of strategies to improve health and healthcare (www.cearegistry.org)

	<ul style="list-style-type: none"> Advocate for inclusion of hepatitis C services in UHC and broader health financing approaches 		
<p>Low awareness of hepatitis C treatment within affected communities & the impact of stigma</p> <ul style="list-style-type: none"> Only 20% of the estimated 71 million persons living with hepatitis C are aware of their infection.(72) Widespread stigma and discrimination,(73) combined with a lack of understanding that hepatitis C is now easily curable, contributes to low testing and treatment coverage.(55) Non-evidence-based restrictive and discriminatory policies and legislation, such as liver-disease stage restrictions and restrictions based on recent drug and/or alcohol use,(74) perpetuate stigmatisation of key risk populations and prevent people from accessing treatment. 	<p>National – Raise awareness of hepatitis C to reduce stigma and increase community demand for testing and treatment:</p> <ul style="list-style-type: none"> Encourage community sector advocacy and civil society engagement to highlight inadequate hepatitis C funding Ensure local epidemiology and surveillance data to inform national hepatitis plans; promote community-focused activities Enable community-led reform of restrictive/stigmatising laws, policies and guidelines (e.g. criminalisation of syringe possession and drug use (75)) <p>International – Raise the profile of hepatitis C, support awareness-raising activities and advocate on behalf of affected communities:</p> <ul style="list-style-type: none"> Advocate for community sector support and funding, including civil society, hepatitis C councils and affected populations Ensure international testing and treatment guidelines (78-81-) support simplified clinical pathways and community-focused responses 	<ul style="list-style-type: none"> World Hepatitis Day events and awareness campaigns No Hep C advocacy tool⁶ 	<p>Brazil (61) Scotland (58) Portugal (76) France (77)</p> <p>Rwanda (36) Pakistan (71) Egypt (82)</p>
<p>Siloed health programmes & poor health infrastructure</p> <ul style="list-style-type: none"> Limited laboratory capacity Lack of reliable supply chains and quality assurance programmes for vaccines, medicines and diagnostics.(39) Inadequate capacity and skills of the health workforce, limit the effectiveness of viral hepatitis programmes.(39, 43) 	<p>National – Implement cost-effective public health systems and strengthen health infrastructure</p> <ul style="list-style-type: none"> Standardise, simplify and decentralise health services for sustainability, cost-efficiency and reach of key-affected populations (1) Coordinate donors towards adopting streamlined policies and guidelines facilitating health system strengthening opportunities and non-siloed program management and delivery Offer training and quality assurance programs for blood safety and infection prevention, laboratory practices, and supply chain management (87) Develop policies and training programs for task-sharing and task-shifting (40, 41) 	<ul style="list-style-type: none"> Global Health Sector Strategy on Viral Hepatitis 2016-2020 (1) WHO Model Essential Medicines List (49) WHO Model Essential In Vitro Diagnostics List (50) Hepatitis testing, treatment and care guidelines (78, 81) Injection safety and blood 	<p>Rwanda (36) Ukraine (37) Georgia (35)</p>

⁶ NoHep.org developed a toolkit for patient organisations, NGOs and individuals working in the field of viral hepatitis to support national advocacy efforts. (<http://www.nohep.org/>)

<ul style="list-style-type: none"> Over-reliance on centralized specialist services or tertiary hospitals, particularly in LMICs,(83, 84) despite clear evidence of the effectiveness of primary care systems for viral hepatitis service delivery.(11, 85, 86) 	<ul style="list-style-type: none"> Strengthen national hepatitis procurement and supply management systems (e.g. through integration into broader national systems or local production pathways) 	<p>safety policies (88)</p>	
	<p>International – Develop global policies and guidelines that facilitate health system strengthening and non-siloed approaches to programme management and delivery:</p> <ul style="list-style-type: none"> Support non-siloed programme funding, enabling integration across related diseases and platforms (e.g. HIV, hepatitis C, TB and vaccination programmes) Review international testing and treatment guidelines (83-86) for simplified clinical pathways and service delivery models Support hepatitis procurement and supply management systems 	<ul style="list-style-type: none"> WHO global guidelines on task shifting (89) 	<p>South Africa (64) Thailand (66) Egypt (47, 48)</p>
<p>Limited access to affordable prevention, diagnostics and medicines</p> <ul style="list-style-type: none"> Despite major reductions in the cost of treatments over the past few years,(10) major discrepancies in prices exist across low, middle and high-income countries.(10, 92) Many countries are missing opportunities to access cheaper medicines through voluntary licenses that allow production and supply of 	<p>National – Negotiate access to affordable diagnostics, prevention and medicines to ensure population coverage and equitable access to treatments:</p> <ul style="list-style-type: none"> Negotiate prices with pharmaceutical companies Include hepatitis C drugs on national Essential Medicines List and Essential In Vitro Diagnostics List Use TRIPS flexibilities and patent challenges Simplify clinical guidelines for cost reduction and testing and treatment decentralisation Comprehensive prevention / harm reduction service packages 	<ul style="list-style-type: none"> Medicines Law & Policy legal and policy analysis hub⁷ 	<p>Egypt (47, 48) Rwanda (36) Malaysia (90, 91)</p>

⁷ Provides policy and legal analysis, best practice models and other information for governments, NGOs, UN agencies and others to assist country negotiations on medicine and diagnostics prices. (www.medicineslawandpolicy.org)

<p>generic antiviral medicines to 112 LMICs.(43)</p> <ul style="list-style-type: none"> • Access to affordable diagnostics is a key barrier for many countries, with diagnostics often costing more than treatment in LMICs, where poor laboratory capacity and access to reliable and low-cost diagnostics prevent rapid scale-up of testing and treatment programmes.(6, 87) 	<p>International – Fund and facilitate access to affordable prevention, diagnostics and medicines and invest in new technologies</p> <ul style="list-style-type: none"> • Support generic competition to drive prices down • Promote mechanisms for affordable medicines acquisition • Accelerate regulatory approval for WHO (or equivalent) prequalified products • Capacity-building for regulatory authorities’ pre-market assessments and registration of new medicines and diagnostics • Encourage private investment funding through innovative blended financing models for low-cost prevention, medicines, and diagnostics’ research and development 	<ul style="list-style-type: none"> • International policies and guidelines, e.g. WHO Essential In Vitro Diagnostics List (50) and Essential Medicines List (93) • Joint price negotiations 	<p>Mercosur countries (94) (Argentina, Brazil, Paraguay and Uruguay)</p>
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FINANCING SOURCE



DOMESTIC FUNDING

- Government health expenditure
- Health insurance
- Taxing commodities
- Maximising effectiveness of public health spending



PRIVATE SECTOR

- Private-Public Partnerships
- Pooled financing
- Results-based financing
- Innovative blended financing models



INTERNATIONAL FUNDERS AND ORGANIZATIONS

- International donor investments
- Cost-sharing strategies
- Social impact bonds and development bonds
- Dedicated hepatitis fund



ACTIVITY



KEY ENABLERS

- Political commitment and advocacy
- Community mobilisation
- Supportive laws, policies and guidelines
- Community-based approaches
- Skilled workforces
- Medicines and equipment
- Research and innovation
- Universal Health Coverage



NATIONAL ACTIVITIES

- National hepatitis plan and local investment case
- Investment and financing for sustainability
- Surveillance and monitoring
- Awareness raising and stigma reduction
- Prevention, testing and treatment
- Health systems strengthening



INTERNATIONAL ACTIVITIES

- Global investment case
- Set and monitor global targets
- International guidelines, guidance and tools
- Facilitate access to affordable prevention, diagnostics and medicines
- Identify and support priority activities
- Invest in new technologies



RETURN ON INVESTMENT



DIRECT ECONOMIC BENEFITS

- Healthcare cost savings
- Disability-adjusted life years averted
- Quality-adjusted life years gained



INDIRECT ECONOMIC BENEFITS

- Workforce and leisure productivity
- Household security
- National and regional security



CROSS - SECTORAL ECONOMIC BENEFITS

- Sustainable Development Goals
- Stronger health systems
- Stronger partnerships and financial mechanisms

Figure 2. Identified challenges to investment in HCV elimination

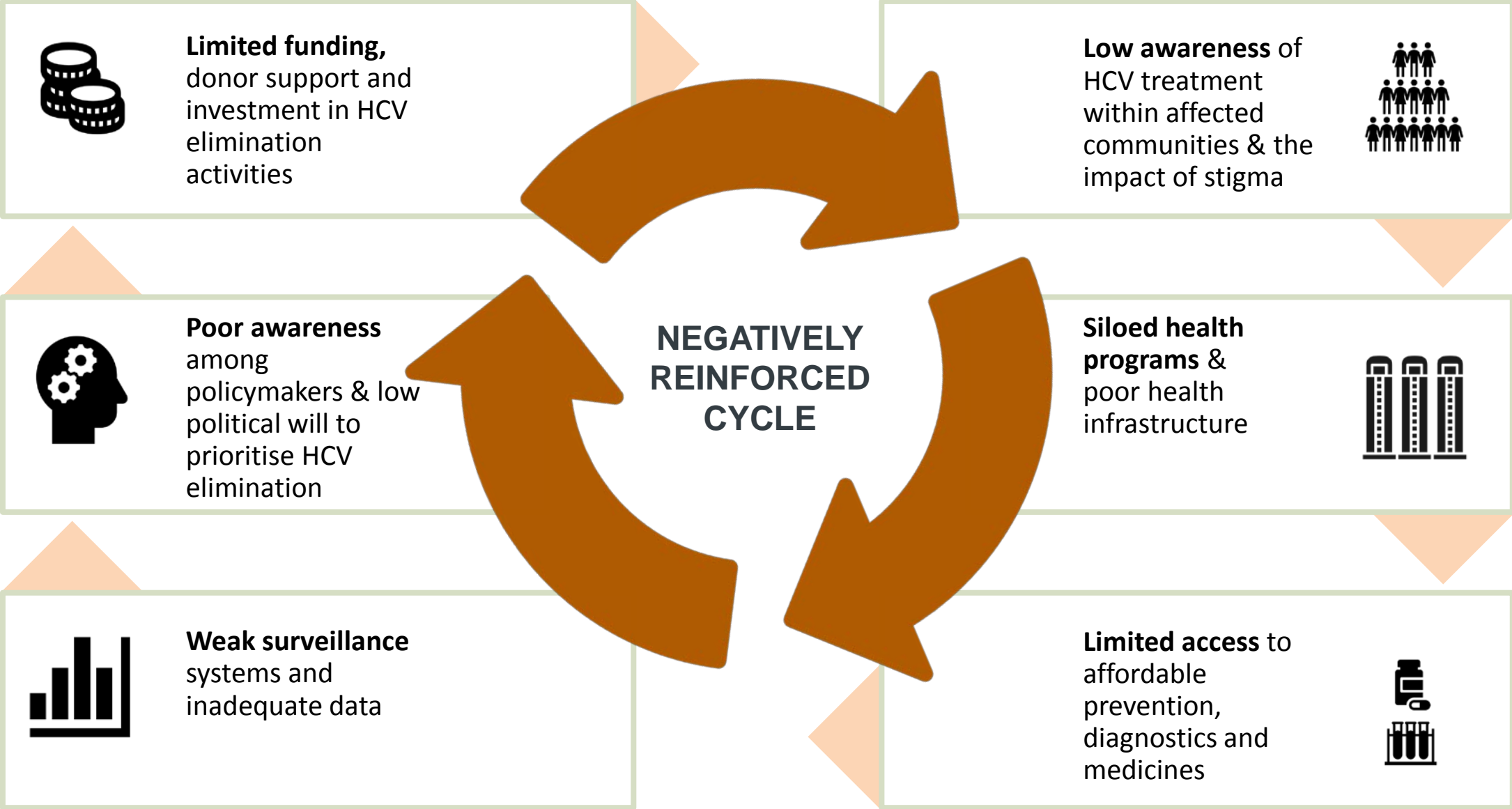


Figure 3. Pathways to scale HCV elimination activities



RAPID SCALE-UP

Interventions where the government is committing significant new HCV resources

RESULTS

- Reprioritize government budgets to scale up HCV activities
- Financing for sustainability - innovative financing to ensure ongoing HCV funding
- Increase the efficiency and effectiveness of HCV programs – targeting new infections



SCALE-UP

Interventions where only limited new HCV resources are available

RESULTS

- Health system strengthening
- Investing in low-cost strategies that increase access to HCV activities
- Investment in research and innovation to improve effectiveness and cost-effectiveness
- Revising guidelines to support task-shifting and program scale up



COST NEUTRAL

Interventions where no new HCV resources are available

RESULTS

- Political commitment & community mobilisation
- National Hepatitis Plan
- Policy change, law reform and guidelines to support HCV elimination
- Price negotiations with manufacturers and use of flexibilities in patent law for low-cost HCV medicines and diagnostics
- Ensuring efficiency of existing resource utilisation and data-driven responses