

The investment case for hepatitis B and C in South Africa: adaptation and innovation in policy analysis for disease program scale-up

Robert Hecht¹, Lindsey Hiebert^{1,*}, Wendy C Spearman², Mark W Sonderup², Teresa Guthrie³, Timothy B Hallett⁴, Shevanthi Nayagam^{4,5}, Homie Razavi⁶, Shan Soe-Lin¹, Kgomotso Vilakazi-Nhlapo⁷, Yogan Pillay⁷ and Stephen Resch⁸

¹Pharos Global Health Advisors, Boston, MA, USA, ²Division of Hepatology, Department of Medicine, University of Cape Town, Cape Town, South Africa, ³Guthrie Health Financing Consultants, Cape Town, South Africa, ⁴Department of Infectious Disease Epidemiology, Imperial College, London, UK, ⁵Division of Digestive Diseases, Imperial College, London, UK, ⁶Center for Disease Analysis, Lafayette, CO, USA, ⁷South Africa National Department of Health, Pretoria, South Africa and ⁸Department of Health Policy and Management, Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Harvard University, Boston, Massachusetts, USA

*Corresponding author. Pharos Global Health Advisors, 780 Boylston Street Suite 16J, Boston, MA 02199, USA.
E-mail: lindsey@pharosglobalhealth.com

Accepted on 30 January 2018

Abstract

Even though WHO has approved global goals for hepatitis elimination, most countries have yet to establish programs for hepatitis B and C, which account for 320 million infections and over a million deaths annually. One reason for this slow response is the paucity of robust, compelling analyses showing that national HBV/HCV programs could have a significant impact on these epidemics and save lives in a cost-effective, affordable manner. In this context, our team used an investment case approach to develop a national hepatitis action plan for South Africa, grounded in a process of intensive engagement of local stakeholders. Costs were estimated for each activity using an ingredients-based, bottom-up costing tool designed by the authors. The health impact and cost-effectiveness of the Action Plan were assessed by simulating its four priority interventions (HBV birth dose vaccination, PMTCT, HBV treatment and HCV treatment) using previously developed models calibrated to South Africa's demographic and epidemic profile. The Action Plan is estimated to require ZAR3.8 billion (US\$294 million) over 2017–2021, about 0.5% of projected government health spending. Treatment scale-up over the initial 5-year period would avert 13 000 HBV-related and 7000 HCV-related deaths. If scale up continues beyond 2021 in line with WHO goals, more than 670 000 new infections, 200 000 HBV-related deaths, and 30 000 HCV-related deaths could be averted. The incremental cost-effectiveness of the Action Plan is estimated at \$3310 per DALY averted, less than the benchmark of half of per capita GDP. Our analysis suggests that the proposed scale-up can be accommodated within South Africa's fiscal space and represents good use of scarce resources. Discussions are ongoing in South Africa on the allocation of budget to hepatitis. Our work illustrates the value and feasibility of using an investment case approach to assess the costs and relative priority of scaling up HBV/HCV services.

Keywords: Disease control, costs, impact, health planning, cost-effectiveness analysis, developing countries, international health policy, planning, policy implementation

Key Messages

- Hepatitis B and C (HBV/HCV) have significant burdens globally and nationally, accounting for >300 million infections and over a million deaths annually worldwide. Despite the advent of new cures for HCV, an expanding array of prevention and treatment options for HBV, and the adoption of ambitious global HBV and HCV targets, few countries have designed or embarked on program scale-up to date.
- South Africa's 5-year National Hepatitis Action Plan is one of the first examples of an investment case that combines tools for costing, impact modelling, cost-effectiveness analysis, and fiscal space analysis for scaled-up HBV and HCV disease control scenarios.
- The South Africa Action Plan investment case shows that carefully selected investments in HBV and HCV can have a significant impact on the twin epidemics, while meeting standard cost-effectiveness criteria and demonstrating affordability amidst government expenditure constraints.
- The South Africa Action Plan experience also shows the importance of an engaged multi-stakeholder process that involves the finance and health ministry and other national interest groups.
- The investment case approach used in South Africa can be adapted to other contexts and can guide other countries looking to synthesize and analyse the evidence needed to consider the advisability of embarking on large scale investments in HBV/HCV.

Introduction: the opportunity and policy barriers to scaling up HBV and HCV treatment

With the advent of new and highly effective cures for hepatitis C (HCV) and an expanding array of preventive and therapeutic interventions for hepatitis B (HBV), there is growing interest among government, advocacy and international partners to mount large-scale national hepatitis control programs. These programs could dramatically reduce the burden of HBV and HCV, which together account for >320 million infections and over 1.24 million deaths annually (World Health Organization 2017). Although ambitious global and regional hepatitis goals exist, notably the elimination of HBV/HCV by 2030 championed by WHO (World Health Organization 2016a), most countries have yet to establish comprehensive national programs to scale up HBV and HCV prevention and treatment.

One reason for the slow action is the paucity of locally informed rigorous analyses estimating the likely cost, health impact, value and feasibility of scaling up national HBV/HCV programs. In addition, there is no immediately available source of large-scale external donor aid for HBV/HCV programs. LMIC countries contemplating HBV/HCV program scale-up will need to focus on mobilizing domestic financial resources for which many other health priorities compete. Under these circumstances, modelling studies of prospective HBV/HCV investments will have to show that hepatitis should be a priority for domestic financing, and these analyses will need to be directed at countries' ministries of finance and health, national health insurance agencies, and other payer institutions.

In this context, our team, composed of leading South African experts and Ministry of Health officials and outside specialists in global health policy and economics, used an investment case approach to design a 5-year National Hepatitis Action Plan for South Africa. This Action Plan assessed the technical and financial feasibility of investments in an expanded HBV/HCV prevention and treatment program that would launch the country on a longer-term trajectory towards possible elimination of HCV and major reductions in the burden of HBV and HCV (Schwartländer *et al.* 2011). This approach was also grounded in a process of intensive engagement of local stakeholders, with national technicians, senior government officials and advocates all heavily involved.

The purpose of this article is to describe the process of developing this Action Plan, present its main methods and results, and elucidate the policy implications of our work for South Africa and other countries. We view this paper as providing a pioneering real-world example for other countries that will also soon be embarking on the road to HBV/HCV national program scale-up.

Epidemiology of HBV and HCV in South Africa

Like many low- and middle-income countries (LMICs), South Africa suffers from a significant burden of HBV and HCV, with over 113 million disability-adjusted life years (DALYs) lost due to hepatitis in 2013 (Stanaway *et al.* 2016). In a recent systematic review based on observational studies performed in the general population, healthcare workers and pregnant women, HBsAg seroprevalence was estimated at 6.7%, pointing to high intermediate endemicity with an estimated 3.5 million individuals chronically HBV infected (Schweitzer *et al.* 2015). While HCV seroprevalence and identifiable risk factors in South Africa are still poorly understood and are being characterized through a number of studies (Scheibe *et al.* 2017), it is currently estimated that just under 1% of the population are chronic carriers of HCV infection (around 400 000 persons) (Ellis *et al.* 1990).

While these numbers are dwarfed by the roughly 12% of South African adults infected with HIV, the burden of liver disease due to HBV and HCV is significant. The lifetime risk of cirrhosis, liver failure and hepatocellular carcinoma is 15–40% for HBV patients and the risk that chronic HCV patients become cirrhotic within 20 years is 15–30%. Each year these HCV patients have a 1–4% risk of developing hepatocellular carcinoma (WHO Africa Regional Office 2016). Most of these people living with HBV and HCV do not know that they are infected, placing them at risk for liver-related morbidity and mortality and increasing the likelihood that they will spread the virus to others (Trépo *et al.* 2014).

South Africa National Hepatitis Action Plan

In the face of this large burden and stimulated by the prospect of new cures for HCV, the South African Department of Health (NDoH) drafted new clinical guidelines for viral hepatitis in 2015–

2016, with the backing from the World Health Organization (World Health Organization 2016b, c). To translate these guidelines into an operational implementation plan, NDOH, in collaboration with this paper's authors, developed a 'Viral Hepatitis National Action Plan' for the 5-year period 2017–2021.

In creating the Action Plan, South Africa sought to answer the following key questions:

1. What set of priority interventions should be included in a hepatitis national program?
2. How much would these investments cost over an initial 5-year period, assuming it would eventually take more than a decade to eliminate HCV and control HBV?
3. If little or no external funding was available and if such a plan had to be financed entirely from domestic public sources, would this be affordable?
4. Would the planned investments represent good value for money for South Africa, given its limited budget resources and many competing demands?
5. Overall, would the combination of spending, impact and projected cost-effectiveness add up to a strong 'investment case' to present to the National Treasury (NT), the South African finance ministry?

The investment case approach

This investment case approach has been widely used in other areas of health, including in assessing proposed investments in national HIV, TB and malaria programs (Schwartzländer *et al.* 2011), but it is in the nascent stages of being applied to HBV and HCV. HCV scale-up has been costed for Georgia, Egypt and Mongolia (Estes *et al.* 2015).

Impact of HCV treatment has been estimated for >50 countries using an approach pioneered by the Center for Disease Analysis, comparing the status quo with the WHO goals of elimination by 2030 (Razavi *et al.* 2014; Bourgeois *et al.* 2016; Hajarizadeh *et al.* 2016; Soipe *et al.* 2016). In addition, the projected impact and cost-effectiveness of interventions for HBV have recently been modelled in China and for HCV in India (Aggarwal *et al.* 2003; Nayagam *et al.* 2016a; World Health Organization 2016a), but there are few if any comprehensive investment cases. Our work in South Africa is one of the first attempts to produce such a national investment case.

Methods and data

Scope

The first step was for our team, composed of South African NDoH officials, local hepatologists, and experts in epidemiological modelling, health economics and financing, to establish the scope and organizing framework for the Action Plan. Using the draft national guidelines, we developed a list of HBV and HCV activities that the NDoH Task Force agreed should be included, and then grouped these activities into thematic categories ('priority areas'). Since the scope of the Action Plan covered a wide range of HBV/HCV prevention and treatment activities, plus improved surveillance, provider training and health communications/demand generation, we consulted >20 South African experts to gather inputs. For each activity, we considered factors including: current level of implementation, feasible rate of scale-up, targets for the 5-year period, prices and unit costs, organizational unit responsible for implementation, as well as contextual factors such as geographical variation or legal and regulatory requirements.

Cost and affordability

To estimate the Action Plan's financial requirements, we created an ingredients-based costing tool. In doing this, we drew upon standard methods which have been used to cost other programs such as the South Africa HIV Investment Case and the National HIV, TB and STI Strategic Plan (UNAIDS; Asian Development Bank 2004; South Africa National Department of Health; South Africa National AIDS Council 2015, 2017).

The tool was implemented in Microsoft Excel and provides templates for program objectives, planned activities, responsible parties, scale-up targets and progress indicators. No primary costing was undertaken, but key stakeholders and service providers were interviewed to obtain the required cost data from existing secondary sources such as reference price lists, expenditure records and prior costing studies.

The tool summarizes costs by objective, activity and calendar year, and breaks down capital, recurrent, fixed, variable and one-time start-up costs. Furthermore, it distinguishes 'additional funds' (e.g. HCV medications) from 'reallocated existing resources' (e.g. time spent by nurses doing counselling and care for hepatitis patients).

The costing approach was from the perspective of the service provider. Available unit costs were multiplied by the estimations of quantities from the epidemiological projections of the numbers in need, which were guided by the annual targets over the 5-year period. Unit prices (ZAR 2016) were assumed to be linear with respect to scale, with no increasing or decreasing returns. Capital investments were annualized over their useful life-years. The exchange rate at end 2016 was used.

To assess affordability and domestic fiscal capacity, we compared the estimated costs of the South Africa National Hepatitis Action Plan with projected annual public-sector budgets for health, looking at both total and incremental funds over the 5-year period, and adjusting for anticipated inflation.

Health impact

To estimate the impact of these investments on the burden of disease in South Africa, we adapted two well-known and widely-accepted disease models.

For HBV, we used the model developed by Imperial College London (Nayagam *et al.* 2016c) which operates dynamically and projects the simultaneous impact of a range of HBV prevention activities (newborn and child vaccination, prevention of mother to child transmission, HBV treatment as prevention) and treatment with anti-virals on number of new infections, cases of cirrhosis and liver cancer, and HBV-related mortality. The model also allows for the simulation of scenarios for scaling up HBV treatment gradually by targeting treatment to individuals in particular demographic groups (e.g. pregnant women, those in certain birth cohorts, etc.) and those with more advanced stages of liver fibrosis.

For HCV, we used the CDA disease model, which links prevalence to screening in order to estimate the size of the screening and diagnosis effort required, and then ties projected treatment with direct acting anti-virals (DAAs) to reductions in chronic HCV prevalence, illness and mortality (Blach *et al.* 2017). This static Markov model assumes constant new infections into the future and does not include a dynamic loop connecting HCV prevention and treatment to incidence. The model does however track disease progression of HCV infections over time.

For both HBV and HCV modelling, we compared the Action Plan scenario to two other scale-up scenarios: the status quo and

WHO Elimination 2030 targets. The status quo scenario represented a ‘no action’ counterfactual—what would happen if no scale-up program was launched and only current efforts were sustained. It assumed there would be no improvements in HBV prevention. Treatment would be limited to the fewer than 1000 patients currently being treated for HBV in South Africa, and the fewer than 500 patients being treated for HCV, most of these in one hospital in Cape Town and the remainder in other major cities.

Since DAAs have not yet been registered with the South African regulatory authority, these few individuals are currently being treated as part of clinical trials or compassionate access programs, importing generic DAAs from India following Medicines Control Council (MCC) Section 21 approval. These small quantities of DAAs are either self-funded, funded by provincial hospitals, or via private health insurance.

The two disease models generate health impacts through five interventions: improved HBV vaccination coverage through expanded routine child immunization, HBV birth dose vaccination, HBV prevention of mother to child transmission (PMTCT), HBV treatment and HCV treatment. Current coverage of routine child immunization, including HBV as one antigen of the hexavalent vaccine, was estimated at baseline at about 70% in South Africa (Nayagam *et al.* 2016c; World Health Organization and UNICEF 2017), and is expected to rise further in the coming years as part of the ongoing national EPI program. The remaining four interventions were prioritized by the NDoH Task Force for inclusion in the Action Plan due to their current low coverage. HBV treatment costs were assumed to include all direct treatment activities and 50% of workforce training. HCV treatment costs were assumed to comprise HCV screening and case finding, treatment itself, and the other 50% of workforce training.

The main health benefits modelled included reductions in mortality; reduced morbidity from averted cases of advanced liver disease, including hepatocellular cancer and cirrhosis; and DALYs averted generated from reductions in mortality and disability (Murray 1994; World Health Organization 2004; Nayagam *et al.* 2016b). Since the onset of sequelae associated with chronic hepatitis is often delayed until later in life, the simulations tracked population outcomes through 2080 for HBV and 2050 for HCV in order to capture the long-term benefits of the activities undertaken in the 5-year Action Plan.

It is reasonable to assume additional benefits would be generated through the activities in the Action Plan that were not explicitly modelled, including reduced transmission of hepatitis A and B in health care facilities, and reduced transmission of hepatitis C in high-risk populations such as injecting drug users. Quantifying the deaths and disability averted from these other benefit streams would further enhance the overall cost-effectiveness of the Action Plan.

Cost-effectiveness analysis and the investment case

We combined our cost estimates and impact analysis to derive selective value-for-money measures. We estimated the cost-effectiveness of the benefits of the overall Action Plan and the incremental cost-effectiveness of each of the four priority interventions (HBV birth dose vaccination, ANC screening for HBsAg with treatment of mothers with high risk of transmission to their child and HBV and HCV treatment). In doing this, we distributed the other cross-cutting costs of the Action Plan equally across the four interventions.

Country-specific studies have shown these four interventions to be generally cost-effective, particularly birth dose vaccination

(Murakami *et al.* 2008; Klingler *et al.* 2012). We anticipated similar results for South Africa, but waited to see the analysis using best estimates of disease burden and prevailing costs, with particular focus on the relative impact and cost-effectiveness of the different interventions, which could help national decision-makers to set priorities within a highly constrained fiscal environment.

To interpret cost-effectiveness and set thresholds for investment decisions, we expressed the incremental cost-effectiveness ratios (ICERs) as a percentage of per capita GDP. While no definitive cost-effective threshold exists for South Africa, recent work suggests that estimates of less than half of per capita GDP are likely to represent good value (Woods *et al.* 2015). Other recent work focusing on the consumption value of health benefits suggests a somewhat higher threshold around 1-2 times per capita GDP (Chang *et al.* 2016; Robinson *et al.* 2017). We consider both of these thresholds in our analysis. In addition, given these diverse views, we provide comparisons to alternative uses of additional health resources in South Africa.

Data sources

Data on the burden of HBV and HCV in South Africa are available from several studies in the general population and in selected subgroups (Burnett *et al.* 2007; Firnhaber *et al.* 2008; Lukhwareni *et al.* 2009; Boyles and Cohen 2011; Andersson *et al.* 2013; Hatzakis *et al.* 2015; Mdlalose *et al.* 2016).

However, more epidemiological data on HBV and HCV are urgently needed for South Africa—several surveys and studies are proposed as part of the Action Plan, including an analysis of hepatitis prevalence in pregnant women as part of South Africa’s long-established HIV antenatal seroprevalence surveillance. Data on unit costs for public awareness, training, surveillance, screening, counselling and lab tests were obtained from government institutions including the National Institute for Communicable Diseases, published sources such as the NDoH price list (South Africa National Department of Health 2016), comparable unit costs from the well-documented South Africa HIV program, and other hepatitis modelling studies for South Africa (Fraser *et al.* 2016). Hepatitis B monovalent immunization costs were based on the prices of vaccines, consumables, and service delivery costs from UNICEF and the South Africa EPI program. The costs of hepatitis medicines were based on the current tender prices for tenofovir and interferon therapy for HBV, and on the price for DAAs for HCV as listed by Gilead Sciences for LMICs in its generic zone.

Licensees of Gilead have been selling DAAs at lower prices in other LMICs, but as of yet they have not registered their products in South Africa. Follow-on analysis could assess the additional savings possible through reduced DAA prices, which would generate lower and more attractive ICERs.

Results

Scope

Based on the consultations described above, it was decided that the Action Plan would cover a wide range of activities to prevent and treat HBV and HCV in South Africa.

Given anticipated fiscal and human resource capacity constraints, moderate coverage targets for HBV and HCV treatment were chosen, below the levels required to achieve the WHO global goals for 2030 (World Health Organization 2016b). Activities that are already ongoing, such as HBV childhood immunization, were

Table 1. Scope of South Africa National Hepatitis Action Plan activities: framework and scale-up targets

Action plan framework	Unit of reach	Scale-up targets				
		2017	2018	2019	2020	2021
Priority Area 1: Raise awareness of Hepatitis infection						
Objective 1a: Raise awareness among health care workers (HCW) of Hepatitis burden and risk, and SA's new national guidelines for prevention, diagnosis, and treatment						
1a1 Develop & distribute brief education materials (IEC flyers) to address known gaps in KPA among current HCW	% of health workers who receive materials	100%	–	100%	–	100%
1a2 Disseminate new national Viral Hepatitis Clinical Guidelines to HCW at all levels	% of health facilities with the guidelines	100%	–	–	–	–
Objective 1b: Train HCWs to deliver guideline-concordant care for viral hepatitis prevention, diagnosis and treatment						
1b1 Develop & implement in-service training workshops reaching targeted staff at PHC & district hospitals	% of health professionals trained	25%	50%	60%	70%	75%
1b2 Integrate a viral hepatitis training module into the curricula of clinical training programs	% of curricula for clinical training institutions with viral hepatitis module	100%	–	–	–	–
Objective 1c: Coordinated National Campaign to Build awareness among the general public & high-risk communities						
1c1 Coordinate with the national campaign (PHILA) and ensure hepatitis inclusion	% of adult population reached	50%	60%	70%	80%	90%
1c2 Produce IEC materials for general population, high risk communities, & all patients at clinics & hospitals	% of adult catchment population around public health facilities reached	80%	30%	20%	10%	10%
1c3 Develop and implement a program for WBOTS/CHWs to educate their communities about hepatitis	% of wards receiving WBOT education	40%	60%	70%	80%	90%
1c4 Promote annual awareness days (World Hepatitis Day—28 July, etc)	Number of events/campaigns executed per annum	10	10	10	10	10
Priority Area 2: Strengthen Knowledge of Hepatitis Burden of Disease						
Objective 2a: Track prevalence of hepatitis infection in general population and sub-populations						
2a1 Include HBsAg and HCV Ab test (HCV VL in Ab+) to at least 1 nationally representative serosurvey every 2–3 years	ANC report with hepatitis prevalence	–	1	–	1	–
2a2 Undertake a retrospective analysis of ANC samples to establish vertical transmission risk of HBV	Vertical hepatitis transmission report	1	–	–	–	–
2a3 Undertake a special survey of high risk populations for HCV, including MSM, CSW, STI patients every 2–3 years	Study of high-risk populations	–	–	1	–	–
2a4 Retrospective analysis of children (<15 years) with measles stored blood samples to ascertain HBV prevalence	Prevalence report	1	–	–	–	–
Objective 2b: Improve surveillance systems and laboratory capacity						
2b1 Provide technical assistance to health facilities & laboratories to improve surveillance data & reporting	% of national and provincial laboratories and all health facilities	50%	80%	100%	100%	100%
Priority Area 3: Prevent transmission of viral hepatitis						
Objective 3a: Minimize risk of Hepatitis A and B transmission risk in health care facilities						
3a1 Enforce pre-employment certification of HBV and HCV carrier status and Hep A and B vaccination	% of health facilities covered	20%	50%	70%	90%	95%
3a2 Undertake 'opt-out' screening of all current HCWs (one-time)	% of healthcare workers screened	20%	50%	60%	70%	85%
3a3 Undertake 'opt-out' screening of all medical/nursing students (every year)	% of students screened	10%	30%	50%	65%	80%
3a4 Ensure access to treatment for HCWs with CHB or CHC	% of healthcare workers identified needing treatment	–	–	100%	100%	100%
3a5 Ensure PEP is available in all public health facilities	% of health facilities covered	20%	50%	70%	85%	95%
Objective 3b: Prevent vertical transmission of HBV						
3b1 Add HBV Birth Dose within 12 h to routine EPI	% coverage of HBV birth dose	–	95%	95%	95%	95%
3b2 Add routine screening for HBsAg and PMTCT treatment to ANC at PHC level	% coverage of HBV screening and PMTCT	–	25%	50%	75%	90%

(continued)

Table 1. (continued)

Action plan framework		Scale-up targets				
Activity	Unit of reach	2017	2018	2019	2020	2021
Priority Area 4: Improve Diagnosis and Treatment of Chronic Hepatitis						
Objective 4a: Routing screening for hepatitis B and C in target populations						
4a1	HBsAg screening in ANC, including household contacts of HBsAg+ ANC cases detected	–	2.5%	50%	70%	90%
4a2	Implement routine screening of high-risk populations for HCV	–	–	10 000	35 000	60 000
Objective 4b: Expand access to treatment for mono-infected CHB						
4b1	Expand access to treatment for mono-infected CHB	2 500	5 000	10 000	17 500	25 000
Objective 4c: Expand access to treatment for CHC						
4c1	Expand access to treatment for CHC	500	1 000	2 000	4 000	8 000
Objective 4d: Training Programs to Increase Hepatology Trained Workforce						
4d1	One-year diploma program for mid-career clinicians	–	5	12	15	20
4d2	Specialist hepatology fellowships	–	2	4	4	4
4d3	Telemedicine program partnership (ECHO Project) with University of New Mexico USA	3	3	6	12	15
Priority Area 5: Management, Coordination, and Evidence-based Policy						
Objective 5a: Ensure integration of Hepatitis efforts into HIV, TB and other related efforts within the DOH						
5a1	Employ adequate management and support staff within NDOH and PDOHs for all aspects of management and coordination of the hepatitis response	50%	70%	90%	100%	100%
Objective 5b: Undertake M&E and strategic information management within the NDOH hepatitis Unit						
5b1	Establish a Hep M&E Unit within the NDOH and routinely collect and consolidate required data elements, based on agreed indicators	100%	100%	100%	100%	100%
Objective 5c: Undertake supervision, quality control and technical support visits to PDOHs and treatment facilities						
5c1	NDOH staff to undertake quarterly site visits to PDOHs and treatment facilities (tertiary and secondary)	50%	60%	75%	95%	100%
Objective 5d: Develop and promote a research agenda for hepatitis in South Africa						
5d1	Identify relevant research and develop a priority research agenda with stakeholders (at an annual workshop), secure funding and ensure coordination between efforts	80%	85%	90%	95%	100%

deemed important but were not included in the Action Plan since they are already operating at scale.

The Action Plan consisted of five main priority areas (Table 1):

1. *Awareness Raising* among the health work force and general population: information campaigns, training of health workers.
2. *Strengthening Knowledge* of disease burden: surveillance, surveys and special studies.
3. *Prevention of Viral Hepatitis*: protection of health care workers, HBV vaccine birth dose and PMTCT.
4. *Testing, Care, and Treatment*: screening, diagnosis, linkage to care, and drug therapy for HBV and HCV.
5. *Management and Coordination*: program management, monitoring and evaluation, and policy development.

Cost and affordability

The overall cost of the 5-year Action Plan was estimated to be ZAR3.78 billion (US\$270 million). The costliest part of the Action Plan was the testing, care, and treatment component, accounting for about ZAR2.47 billion (US\$177 million) or 65% of the total, followed by prevention (15%), awareness raising (11%), strengthening knowledge (6%) and management and coordination (2%).

Among the high impact investments, HBV birth dose vaccination and PMTCT were estimated to cost ZAR512 million (US\$36.5 million), a one-time campaign to screen and vaccinate health workers would absorb ZAR56 million (US\$4.0 million), and initial scale up of HCV and HBV treatment would require ZAR594 million (US\$42.4 million) and ZAR1.66 billion (US\$114.2 million), respectively, over 2017–2021 (Table 2).

Our fiscal analysis suggests that investments under the Hepatitis Action Plan amounts to an average of about 0.5% of the total ZAR771 billion (US\$55.0 billion) projected government expenditures for health during 2017–2021. Based on the Government's own forecast of modest growth of the South African budget of 3.5% over this period, the required outlays under the Action Plan would absorb an average of 14% of the anticipated increment in government spending.

To put the estimated price tag for the Action Plan in perspective, South Africa currently spends nearly ZAR19 billion (US\$1.36 billion) annually to combat HIV and AIDS (South Africa National AIDS Council 2017). The cost of the Hepatitis Action Plan thus represents <4% of the funds that the South African Government expects to devote to HIV over the next 5 years.

Impact

Using our disease models, we found that the investments outlined in the Action Plan, if sustained during the 5-year period and beyond, can have a major impact on the HBV and HCV burden of disease in South Africa.

Under the status quo, we estimated that 1.1 million new HBV infections would occur over the next six decades until 2080, with 393 000 HBV-related deaths and losses of 15 million DALYs. By investing in the Action Plan over the next 5 years, 10% of these losses would be averted. Going beyond this start to reach the ambitious WHO targets (30% reduction in new infections by 2020, 90% by 2030) would avert up to 30% of the losses expected under the status quo.

Although not explicitly included in the Action Plan, improving the coverage of South Africa's routine child vaccination program (currently at about 70% (Nayagam, et al. 2016; World Health Organization and UNICEF 2017)) to 90% was estimated to result

in a 25% reduction in new HBV infections, as compared with the status quo.

Adding birth dose vaccination (within 24 h of birth) to 90% coverage levels would avert another 35% of new infections, and screening of pregnant women and tenofovir treatment for those found to be HBV-infected would lead to a further 3% drop in incidence. The combined effect of these measures was thus estimated to lower new infections by 63% over the next 60 years.

Implementing the 5-year effort to begin screening and treating South Africans with chronic HBV during 2017–2021 would avert an additional 13 000 liver disease-related deaths, including 2000 cases of liver cancer, and result in a savings of an additional 66 000 discounted DALYs compared to only the prevention activities. Sustaining this effort and increasing the pace of scale up to achieve the WHO goals by 2030—assuming that this is feasible for South Africa in terms of fiscal and human resource capacity—would multiply these initial gains 15-fold, averting nearly 200 000 deaths and over 31 000 cases of liver cancer.

The proposed initial five-year scale up of HCV treatment of 15 500 patients would result in up to an estimated 7145 additional deaths averted and 64 000 DALYs saved as compared with the status quo, depending on the targeting strategy. If this early effort was sustained to enable South Africa to achieve the WHO goal of elimination by 2030, the country could avert over 30 000 HCV-related deaths.

Cost-effectiveness

Our analysis suggests an overall cost-effectiveness ratio of US\$3310 (ZAR46 373) per DALY averted for the full Action Plan, demonstrating acceptable value-for-money, as this ratio is just below benchmark of half per capita GDP (South Africa's 2015 GDP per capita = US\$7620) (Table 3). While the Action Plan's cost-effectiveness profile is less favourable than that of some key programs in South Africa, such as AIDS treatment and TB treatment (Meyer-Rath et al. 2017; Tufts Medical Center 2018), it is similar to other health interventions under consideration for implementation in South Africa including: pre-exposure prophylaxis for HIV: \$2700 per life year saved (Walensky et al. 2012); strategies for rural community-based TB/HIV screening and linkage: \$1700–\$3400 per life year saved (Gilbert et al. 2016); screening for TB in HIV patients: \$2800 per life year saved for sputum smear, \$5100 per life year saved for Xpert/RIF (Andrews et al. 2012); and a diabetes education program: \$1862 per QALY gained (Mash et al. 2015).

Among the individual interventions, HBV birth dose was the best buy at US\$329 (ZAR4609) per additional DALY averted compared to the status quo. The ICERs for HCV and HBV treatment were US\$2849 (ZAR39 914) and US\$5021 (ZAR70 344) per additional DALY averted, respectively (Table 3). The current estimates are based on no restrictions on treatment eligibility, but if South Africa pursued a more targeted approach focusing on more advanced patients, HCV treatment could become more cost-effective.

PMTCT was found to be the least cost-effective impact intervention [ICER of US\$26 241 (ZAR367 636) per DALY averted] (Table 3). However, PMTCT was not removed from the analysis, because it was the main source of case finding for the HBV treatment program in the Action Plan. Thus, when it is bundled with HBV treatment, the ICER for the combined package of PMTCT and HBV treatment was a more reasonable US\$5531 (ZAR77 489) per DALY averted.

Table 2. Cost breakdown by Action Plan priority areas and objectives (in ZAR millions)

		2017	2018	2019	2020	2021	ZAR M (USD M)
Priority Area 1	Raise awareness of hepatitis infection	76	89	100	77	92	434 (31)
Objective 1a	Raise awareness among health care workers of Hepatitis burden and risk, and SA's new national guidelines	0.1	0	0.04	0	0.04	0.2
Objective 1b	Train HCWs to deliver guideline-concordant care for viral hepatitis prevention, diagnosis and treatment	6	6	6	6	6	30
Objective 1c	Coordinated national campaign to build awareness among the general public & high-risk communities	70	84	94	71	85	404
Priority Area 2	Strengthen knowledge of hepatitis burden of disease	45	92	3	103	0.8	244 (18)
Objective 2a	Track prevalence of hepatitis infection in general and sub-populations	44	92	2	102	0	240
Objective 2b	Improve surveillance systems and laboratory capacity	0.4	0.6	0.7	0.8	0.8	3
Priority Area 3	Prevent transmission of viral hepatitis	9	12	164	175	208	568 (41)
Objective 3a	Minimize risk of Hep A & B transmission risk in healthcare facilities	2	2	46	3	3	56
Objective 3b	Prevent vertical transmission of HBV	8	10	118	172	205	512
Priority Area 4	Improve diagnosis and treatment of chronic hepatitis	107	202	390	703	1071	2473 (177)
Objective 4a	Routing screening for HBV and HCV in target populations	0	0	7	22	33	62
Objective 4b	Expand access to treatment for mono-infected CHB	74	147	274	480	686	1661
Objective 4c	Expand access to treatment for CHC	18	38	76	154	308	594
Objective 4d	Training programs to increase hepatology trained workforce	15	17	33	48	45	157
Priority Area 5	Management, coordination, and evidence-based policy	8	10	12	14	15	59 (4)
Objective 5a	Ensure integration of Hepatitis efforts into HIV, TB and other related efforts within the DOH	5	7	9	11	11	44
Objective 5b	Undertake M&E and strategic information management within the NDOH Hepatitis Unit	2	2	2	2	2	9
Objective 5c	Undertake supervision, quality control and technical support visits to PDOHs and treatment facilities	0.6	0.7	1	1	1	5
Objective 5d	Develop and promote a research agenda for hepatitis	0.1	0.1	0.1	0.2	0.2	0.7
Total ZAR M (USD M)		245 (18)	405 (29)	670 (45)	1074 (70)	1387 (88)	3781 (249)

Note: Rows and columns may not sum to total amounts due to rounding.

Table 3. Cost-effectiveness of South Africa National Hepatitis Action Plan interventions

Intervention	Incremental DALYs averted	Incremental cost (USD Millions, discounted 3%)	ICER (USD Millions per additional DALY averted)
Status Quo	-	-	-
Birth Dose	47 185	\$15.5	\$329
HCV Treatment	20 822	\$59.3	\$2849
HBV Treatment ^a	66 191	\$332.3	\$5021
PMTCT	1612	\$42.3	\$26 241
Overall	135 810	\$449.5	\$3310

^aAnalysis accounts for the lifelong tenofovir treatment for surviving HBV patients, while the costs for HBV treatment described in Table 2 only cover the 5-year cost of the Action Plan.

Discussion

The modelling and analysis of the costs, financing, expected impact, and cost-effectiveness of the proposed 2017–2021 South African National Hepatitis Action Plan suggests that South Africa can mount an expanded response to HBV and HCV at an affordable cost and in a cost-effective manner. Even if a wide range of demand generation, surveillance, prevention and treatment activities are undertaken, the financial resources required amount to ZAR3.78

billion over 5 years, or around 0.5% of all projected government health spending in South Africa. The modelled impact of this first 5-year investment is significant, at 13 000 deaths averted from HBV and another 7000 from HCV. The Action Plan investments put South Africa on the path to a large-scale reduction of HBV and HCV, with the potential to avert >672 000 HBV infections and save a total of 60 000 lives from liver-related disease caused by HCV if the treatment program continues to expand and achieves elimination by 2030, as proposed by WHO (World Health Organization 2016b).

If South Africa is unable to mobilize the full funding requirements for the Action Plan because of fiscal pressures, our analysis shows how it can nevertheless target a sub-set of priority activities with important benefits. Implementing HBV birth dose vaccination should be the first priority, based on the highest cost-effectiveness and low budgetary cost of ZAR46 million (US\$3.3 million) over 5 years. HCV and HBV treatment could then be phased in, starting with the modest coverage suggested in the Action Plan and expanding progressively over time.

HBV PMTCT as a standalone prevention activity was not found to be convincingly cost-effective, but should still be considered for inclusion in the overall program since PMTCT screening is currently the main source of HBV case finding, and can be phased in rapidly as an add-on to the existing nationwide PMTCT program for HIV. PMTCT can also serve as a safety net to prevent vertical

transmission if birth dose implementation falters and is a gateway to treatment for young women identified through screening.

The proposed targets for HCV treatment with DAAs, which have a cure rate of over 95% based on three months of daily oral drug therapy, carry a price tag of ZAR600 million (US\$42.4 million) for the first 5 years of program start-up. Assuming that other constraints including health workforce capacity and regulatory approvals can be addressed (see below), such an HCV treatment effort to reach the first 15 500 South Africans with DAAs is both feasible and can yield useful lessons in how to organize and prepare for scale-up. Affordability of HCV treatment could be further enhanced if South Africa obtains DAAs at competitive generic prices. Our modelling assumed a current 'ceiling' price of US\$900 per cure offered by the originator company in the generic zone to which South Africa belongs. Prices as low as \$200–\$450 per cure are being reported from India and Egypt, where generic licensees are competing with each other. South Africa may be able to procure DAAs at prices in this range (World Health Organization 2017).

HBV treatment scale up was also estimated to be cost-effective, based on the low cost of the generic form of the recommended drug of choice (tenofovir). The large burden of HBV disease (6–7% in the general population) also argues in favour of launching a treatment program. However, given the relatively large share of HBV treatment in the overall cost of the Action Plan and the more complex and demanding requirements for patient staging, diagnosis and monitoring, this could be an area where South Africa proceeds more slowly in the next few years if it is unable to pursue all of the investments in the Action Plan simultaneously.

The feasibility of implementing the Action Plan may be enhanced if South Africa builds its hepatitis program on the backbone of the existing health system, especially the parts of the system that have been strengthened over the past two decades to address maternal and child health and HIV/AIDS. A new birth dose vaccination component can be inserted into the current post-partum services being offered in health facilities, including the BCG vaccine that is given at birth. The screening and antiviral treatment for HBV-positive pregnant women can be added on to antenatal services that already screen and use anti-retroviral prophylaxis for HIV-positive pregnant women in South Africa (up to 30% of these women are testing HIV positive). Screening for HBV and HCV can also be added on to existing screening, counselling, and referral services for HIV and tuberculosis that have been decentralized to primary health care facilities and special programs catering to high risk sub-populations, such as opioid substitution therapy. The latter could improve the targeting of HCV screening, since emerging evidence suggests a higher prevalence of hepatitis among injecting drug users and other high-risk groups (Scheibe *et al.* 2017).

Even if the financial resources for the Action Plan can be successfully mobilized in South Africa, other important non-financial barriers will have to be addressed. The shortage of trained health workers is one of the most pressing. At the lower levels of the health system, South Africa's community health workers, nurses and primary care physicians will need to be trained to do HBV/HCV testing, counselling, initiation of treatment and patient monitoring. At the upper end of the health system, there is an acute shortage of hepatologists and gastroenterologists—South Africa currently has just a handful of hepatologists who can help to design treatment protocols, train generalist doctors and manage complex cases. Programs such as the ECHO project (University of New Mexico School of Medicine 2017) or simplification of treatment protocols so that general practitioners can treat HBV and HCV patients, could be adopted to ease this constraint.

The other issue is the slowness of the South African drug regulatory authority to register DAAs for HCV treatment. At present, it is taking more than 2 years to register the first originator products. The dossier for Gilead's Sovaldi was submitted in 2014 and approval is expected shortly. However, the file for Harvoni had to be re-submitted in late 2016, and approval was not anticipated for at least 18 months. The other originator products from Merck and Abbvie have not yet been submitted to the MCC. Generic versions of these drugs cannot be registered until after the originator product has been approved. Expedited action by the MCC could overcome this key remaining barrier to large-scale treatment.

While the cost and impact modelling results presented here are solidly grounded on the best available data, there are limitations to our analysis. Our proposed coverage levels and modelled impacts of prevention and treatment interventions are based on assumed HBV and HCV prevalence, which is still poorly understood for South Africa. More surveillance and epidemiological data (seroprevalence and risk factor surveys of the general population, children and pregnant women and high-risk groups) are needed. Due to the disease model design, the HCV health impact estimates do not account for changes in incidence over time due to scaled-up treatment and thus reductions in transmission within at-risk populations. However, in South Africa, where most HCV infections occurred in the past due to unsafe blood transfusions and possible unsafe traditional practices, this feedback loop may be less important, even though there is mounting evidence of some new HCV infections taking place within vulnerable groups, including injecting drug users and men having sex with men (Scheibe *et al.* 2017). Our cost estimates could also benefit from further data collection and validation—a national hepatitis unit cost database, regularly updated, would be a helpful addition to our existing knowledge foundation and could help support future planning efforts.

For HCV drugs, we used current prices charged by the originator company in its generic territories (US\$900 for ledipasvir/sofosbuvir) and for most lab tests we relied on the prices listed by the National Health Laboratory Services. In both drugs and diagnostics, we expect prices to fall over time as generic competition increases and volumes grow. This will make the Action Plan less costly and enhance cost-effectiveness further. Our analysis could then need to be updated to incorporate these efficiency gains.

The modelling suite we used provides a decision-making instrument for other LMIC governments and potential donors. Next steps would be adding a user-friendly interface to the disease modelling component and enhancements to the costing tool to make it more accessible to first-time users.

The South African experience with the Hepatitis Action Plan has important implications for hepatitis policy development. Using an investment case framework, expanded HBV prevention and drug therapy and HCV treatment using the new DAA cures appear to be cost-effective and affordable for South Africa, and this conclusion may apply to other countries. If this turns out to be the case, hepatitis control and elimination efforts may emerge as priorities for future investment, even in LMICs where donor financial support is unlikely to materialize. However, cost-effectiveness and affordability need to be demonstrated in each unique country using locally available data, and neither cost-effectiveness nor affordability can be assumed from the outset. There may be national circumstances of low HBV/HCV prevalence where it is difficult and costly to screen and treat those infected with HBV/HCV, and here an investment case analysis could suggest that hepatitis scale up should not be treated as a priority unless ways are found to make the program more efficient.

In addition, our work demonstrates that the investment case approach, through adapting existing methods while developing new tools for hepatitis, is an appropriate and fruitful method for conducting feasibility analysis and engaging national and international stakeholders in an evidence-based discussion of the advisability of pursuing a range of scenarios for scaling up HBV/HCV programs.

A number of the process elements used in South Africa—including forming a national working group; linking the development of national clinical guidelines with a 5-year action plan and longer-term modelling of scale up; and then bringing the emerging results to the health ministry leadership and a joint health–finance consultative discussion—were productive and could be adopted by other countries.

As growing numbers of countries consider pursuing the WHO goals for HBV/HCV elimination by 2030, the investment case approach that we piloted in South Africa may offer useful lessons on the tools, techniques and engagement process that could be pursued elsewhere to design and adopt national hepatitis programs and mobilize the needed resources to prevent disease and save lives.

Acknowledgements

The authors wish to thank the members of the South Africa Viral Hepatitis Working Group for their collaboration, and the World Health Organization office in Pretoria, especially Dr. Augustin Ntlivamunda, for his early partnership on the national guidelines and Action Plan. We are also grateful to Dr. Mark Blecher and his colleagues in the South Africa National Treasury for their feedback on a draft of the National Hepatitis Action Plan.

Funding

The project was supported by a grant from Gilead Sciences, Foster City, CA.

Conflict of interest statement. None declared.

References

- Aggarwal R, Ghoshal UC, Naik SR. 2003. Assessment of cost-effectiveness of universal hepatitis B immunization in a low-income country with intermediate endemicity using a Markov model. *Journal of Hepatology* 38: 215–22.
- Andersson MI, Maponga TG, Ijaz S *et al.* 2013. The epidemiology of hepatitis B virus infection in HIV-infected and HIV-uninfected pregnant women in the Western Cape, South Africa. *Vaccine* 31: 5579–84.
- Andrews JR, Lawn SD, Rusu C *et al.* 2012. The cost-effectiveness of routine tuberculosis screening with Xpert MTB/RIF prior to initiation of antiretroviral therapy: a model-based analysis. *AIDS (London, England)* 26: 987–95.
- Blach S, Zeuzem S, Manns M *et al.* 2017. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *The Lancet Gastroenterology & Hepatology* 2: 161–76.
- Bourgeois S, Blach S, Blach C *et al.* 2016. Achieving WHO recommendations for hepatitis C virus elimination in Belgium. *Acta Gastro-Enterologica Belgica* 79: 222–6.
- Boyles TH, Cohen K. 2011. The prevalence of hepatitis B infection in a rural South African HIV clinic. *SAMJ South African Medical Journal* 101: 470–1.
- Burnett RJ, Ngobeni JM, François G *et al.* 2007. Increased exposure to hepatitis B virus infection in HIV-positive South African antenatal women. *International Journal of STD & AIDS* 18: 152–6.
- Chang AY, Robinson LA, Hammit JK *et al.* 2016. Economics in “Global Health 2035”: a sensitivity analysis of the value of a life year estimates. *Journal of Global Health. Edinburgh University Global Health Society* 7: 10401.
- Ellis LA, Brown D, Conradie JD *et al.* 1990. Prevalence of hepatitis C in South Africa: detection of anti-HCV in recent and stored serum. *Journal of Medical Virology* 32: 249–51.
- Estes C, Abdel-Kareem M, Abdel-Razek W *et al.* 2015. Economic burden of hepatitis C in Egypt: the future impact of highly effective therapies. *Alimentary Pharmacological Therapy* 42: 696–706. Available at: <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=ovftq&NEWS=N&AN=00001716-201509010-00005>.
- Firnhaber C, Reyneke A, Schulze D *et al.* 2008. The prevalence of hepatitis B co-infection in a South African urban government HIV clinic. *South African Medical Journal* 98: 541–4.
- Fraser I, Burger J, Lubbe M *et al.* 2016. Cost-effectiveness modelling of sofosbuvir-containing regimens for chronic genotype 5 hepatitis C virus infection in South Africa. *PharmacoEconomics* 34: 403–17.
- Gilbert JA, Sheno SV, Moll AP *et al.* 2016. Cost-effectiveness of community-based TB/HIV screening and linkage to care in rural South Africa. *PLoS ONE. Public Library of Science* 11: e0165614. <https://doi.org/10.1371/journal.pone.0165614>.
- Hajarizadeh B, Razavi-Shearer D, Merat S *et al.* 2016. Liver disease burden of hepatitis C virus infection in Iran and the potential impact of various treatment strategies on the disease burden. *Hepatitis Monthly* 16: e37234.
- Hatzakis A, Chulanov V, Gadano AC *et al.* 2015. The present and future disease burden of hepatitis C virus (HCV) infections with today’s treatment paradigm - Volume 2. *Journal of Viral Hepatitis* 22: 26–45.
- Klingler C, Thoumi AI, Mrithinjayam VS. 2012. Cost-effectiveness analysis of an additional birth dose of Hepatitis B vaccine to prevent perinatal transmission in a medical setting in Mozambique. *Vaccine* 31: 252–9.
- Lukhwareni A, Burnett RJ, Selabe SG *et al.* 2009. Increased detection of HBV DNA in HBsAg-positive and HBsAg-negative South African HIV/AIDS patients enrolling for highly active antiretroviral therapy at a tertiary hospital. *Journal of Medical Virology* 81: 406–12.
- Mash R, Kroukamp R, Gaziano T *et al.* 2015. Cost-effectiveness of a diabetes group education program delivered by health promoters with a guiding style in underserved communities in Cape Town, South Africa. *Patient Education and Counseling* 98: 622–6.
- Mdlalose N, Parboosing R, Moodley P. 2016. The prevalence of hepatitis B virus infection in HIV-positive and HIV-negative infants: KwaZulu-Natal, South Africa. *African Journal of Laboratory Medicine* 5: 8–12.
- Meyer-Rath G, van Rensburg C, Larson B *et al.* 2017. Revealed willingness-to-pay versus standard cost-effectiveness thresholds: evidence from the South African HIV Investment Case. *PLoS ONE*. 12: e0186496.
- Murakami H, Van Cuong N, Huynh L *et al.* 2008. Implementation of and costs associated with providing a birth-dose of hepatitis B vaccine in Viet Nam. *Vaccine* 26: 1411–9.
- Murray CJL. 1994. Quantifying the burden of disease: the technical basis for disability-adjusted life years. *Bulletin of the World Health Organization* 72: 429–45.
- Nayagam S, Chan P, Zhao K *et al.* 2016a. Investment case for a comprehensive package of interventions against hepatitis B in China. *Journal of Hepatology* 64: S469.
- Nayagam S, Conteh L, Sicuri E *et al.* 2016b. Cost-effectiveness of community-based screening and treatment for chronic hepatitis B in The Gambia: an economic modelling analysis. *The Lancet Global Health* 4: e568–78.
- Nayagam S, Thursz M, Sicuri E *et al.* 2016c. Requirements for global elimination of hepatitis B: a modelling study. *The Lancet Infectious Diseases* 16: 1399–408.
- Razavi H, Waked I, Sarrazin C *et al.* 2014. The present and future disease burden of hepatitis C virus (HCV) infection with today’s treatment paradigm. *Journal of Viral Hepatitis* 21: 34–59.
- Robinson LA, Hammit JK, Chang AY *et al.* 2017. Understanding and improving the one and three times GDP per capita cost-effectiveness thresholds. *Health Policy and Planning* 32: 141–5.
- Scheibe A *et al.* (2017) Programmatic surveillance of viral hepatitis and HIV co-infection among key populations from seven South African cities: data to inform an unmet need, 8th South African AIDS Conference, Durban, South Africa.

- Schwartländer B, Stover J, Hallett T *et al.* 2011. Towards an improved investment approach for an effective response to HIV/AIDS. *The Lancet* 377: 2031–41.
- Schweitzer A, Horn J, Mikolajczyk RT *et al.* 2015. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *The Lancet* 386: 1546–55.
- Soipe AI, Razavi H, Razavi-Shearer D *et al.* 2016. Chronic hepatitis C virus (HCV) burden in Rhode Island: modelling treatment scale-up and elimination. *Epidemiology and Infection* 144: 3376–86.
- South Africa National AIDS Council (2017) National Strategic Plan on HIV, TB, and STIs 2017–2022.
- South Africa National Department of Health (2016) Database of Medicine Prices May 2016. Available at: <http://www.mpr.gov.za/PublishedDocuments.aspx>.
- South Africa National Department of Health; South Africa National AIDS Council (2015) South Africa HIV Investment Case.
- Stanaway JD, Flaxman AD, Naghavi M *et al.* 2016. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *The Lancet* 388: 1081–8.
- Trépo C, Chan HLY, Lok A. 2014. Hepatitis B virus infection. *Lancet* 384: 2053–63.
- Tufts Medical Center (2018) Global health cost-effectiveness analysis registry. Available at: http://healthconomics.tuftsmedicalcenter.org/orchard/search/results?query0=&rule0=OR&query1=&rule1=OR&query2=&super_region=All+Super+Regions®ion=All+Regions&country=All+Countries&country_=South+Africa&publication_da, accessed 18 January 2018.
- UNAIDS; Asian Development Bank (2004) Costing Guidelines for HIV/AIDS Intervention Strategies.
- University of New Mexico School of Medicine (2017) Project ECHO: Hepatitis C Community. Available at <https://echo.unm.edu/nm-teleecho-clinics/hepatitis-c-community-clinic/>.
- Walensky RP, Park J-E, Wood R *et al.* 2012. The cost-effectiveness of pre-exposure prophylaxis for HIV infection in South African women. *Clinical Infectious Diseases*: 54: 1504–13.
- WHO Africa Regional Office (2016) Prevention, Care, and Treatment of Viral Hepatitis in the African Region: Framework for Action, 2016–2020.
- Woods B, Revill P, Sculpher M, Claxton K (2015) CHE Research Paper 109. Center for Health Economics, University of York, York, pp. 1–109.
- World Health Organization (2004) Global burden of disease 2004 update: Disability weights for diseases and conditions. Available at http://www.who.int/healthinfo/global_burden_disease/GBD2004_DisabilityWeights.pdf.
- World Health Organization (2016a) Combating hepatitis B and C to reach elimination by 2030. Available at http://apps.who.int/iris/bitstream/10665/206453/1/WHO_HIV_2016.04_eng.pdf?ua=1.
- World Health Organization (2016b) Global health sector strategy on viral hepatitis 2016–2021. Global Hepatitis Programme Department of HIV/AIDS, (June), p. 56.
- World Health Organization (2016c) Guidelines for the Screening Care and Treatment of Persons with Chronic Hepatitis C Infection, Guidelines for the Screening Care and Treatment of Persons with Chronic Hepatitis C Infection: Updated Version. Available at <http://www.ncbi.nlm.nih.gov/pubmed/27227200>.
- World Health Organization (2017) Global Hepatitis Report 2017. Geneva. Available at <http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1>.
- World Health Organization and UNICEF (2017) South Africa: WHO and UNICEF estimates of immunization coverage: 2016 revision. Available at https://data.unicef.org/wp-content/uploads/country_profiles/South_Africa/immunization_country_profiles/immunization_zaf.pdf.