

# Public health and economic impact of meningococcal conjugate (MCV4) vaccination in the South African HIV-positive population

M de Necker,<sup>1</sup> BComm (Econ), BComm Hons (Econ); J C de Beer,<sup>1</sup> MEng (Electrical Electronic); T Marais,<sup>2</sup> MD

<sup>1</sup> TCD Outcomes Research, Centurion, South Africa

<sup>2</sup> Sanofi Pasteur, Midrand, South Africa

Corresponding author: J C de Beer ([janina@valueinresearch.com](mailto:janina@valueinresearch.com))

**Background.** HIV/AIDS places a large burden on the South African (SA) healthcare system. Such patients are at a significantly higher risk of contracting invasive meningococcal disease (IMD) than immunocompetent individuals. The meningococcal conjugate vaccine (MCV4) is indicated for vaccination against IMD.

**Objectives.** Given the large HIV-positive population in SA, coupled with their increased risk of contracting IMD, the current study analysed the costs and benefits of introduction of the MCV4 vaccine in the SA public-sector HIV-positive population on antiretroviral treatment.

**Methods.** Dynamic Markov models were developed to model the introduction of the MCV4 vaccine, with a target uptake of 50% over 85 years. Most data were sourced from published literature, with some inputs sourced via Delphi panel consensus.

**Results.** The public health results indicate that 39 185 cases of IMD (31 355 without sequelae and 7 830 with long-term sequelae) and 1 780 disease-related deaths could be avoided. There was an approximately ZAR47.6 million reduction in indirect costs, but an increase in total cost of approximately ZAR4.485 billion, due to vaccination costs. A base case incremental cost-effectiveness ratio per quality-adjusted life year of ZAR613 805 was obtained.

**Conclusion.** Significant public health benefits can be achieved by the introduction of the MCV4 vaccine into the public sector for HIV-positive patients on treatment. However, at current low disease incidence rates, introduction of the vaccine would be at a substantially increased cost to the healthcare system.

*South Afr J Pub Health* 2019;3(4):61-65. <https://doi.org/10.7196/SHS.2019.v3.i4.89>

HIV/AIDS places a large burden on the South African (SA) healthcare system, with approximately 7.1 million adults and children in the country living with the disease in 2016.<sup>[1]</sup> According to the National Institute for Communicable Diseases, invasive meningococcal disease (IMD) (caused by *Neisseria meningitidis*) currently has a rare disease incidence of 0.24 cases per 100 000 population (2017).<sup>[2]</sup> HIV-infected individuals, however, exhibit an increased risk of contracting meningococcal disease (11.3 age-adjusted relative risk for HIV-infected v. HIV-uninfected individuals in SA), with an increased case-fatality ratio (odds ratio of 2.1 for HIV-infected v. HIV-uninfected individuals).<sup>[3]</sup> Studies performed elsewhere support this trend in IMD incidence in HIV-infected individuals compared with HIV-uninfected individuals.<sup>[4,5]</sup>

In SA, the meningococcal conjugate vaccine MCV4 (Menactra, Sanofi Pasteur) provides protection against four serogroups, namely A, C, Y and W.<sup>[6]</sup> In the HIV-positive population, two doses of the vaccine are recommended, 8 - 12 weeks apart, followed by lifelong booster vaccinations every 5 years.<sup>[6,7]</sup> It is indicated for use in persons from 9 months to 55 years of age.<sup>[6]</sup> Safety and immunogenicity have been proven in HIV-positive children and

adults, with CD4 counts >25%,<sup>[6]</sup> therefore the introduction of the vaccine is aimed at HIV-positive patients who are well controlled on antiretroviral (ARV) treatment.

Based on the large HIV-positive population in SA, coupled with their increased risk of contracting IMD, there was a need to conduct a study to analyse the costs and benefits of introduction of the MCV4 vaccine in the SA HIV-positive population. The public-sector population in SA was specifically targeted.

## Methods

Dynamic Markov models were constructed in Excel (Microsoft, USA) to model the cost-effectiveness of a cohort receiving the MCV4 vaccine versus a cohort who did not receive an MCV4 vaccine. The Markov process modelled the transition of HIV-positive persons on ARV treatment in the SA public-sector population.

Patients from 0 to 55 years of age were included in the model and followed over an 85-year period (lifetime model). The model has a 3-month cycle length. Two scenarios were compared: 100% of the population not vaccinated with MCV4 v. a calculated uptake percentage of persons vaccinated plus the remainder

not vaccinated with MCV4. A linear uptake strategy was used to calculate the percentage uptake in each year, using a user-defined percentage uptake in the first cycle, and the target percentage to be vaccinated after 85 years. For the base case model, the percentage of patients vaccinated in the first cycle was set to 2%, and the target vaccination uptake after 85 years was set to 50%.

The model has six main health states: no IMD; IMD without long-term sequelae; IMD with long-term sequelae; no IMD, but patient has long-term sequelae from previous IMD; death due to IMD; and non-related death.

Newly diagnosed HIV-positive patients are added to the model at the start of every model cycle. A 5% discount rate for cost and effectiveness was used, in line with SA pharmaco-economic guidelines.

The majority of the data were sourced from published literature. Where published data were not available, a Delphi panel method was used to obtain consensus from a group of five panellists.<sup>[8]</sup> The panellists included key opinion leaders (KOLs) in their respective fields. These include infectious disease and HIV specialists, public health specialists, specialists in vaccine-preventable diseases, as well as microbiology and molecular biology.

## Epidemiology

A case fatality rate of 20% for IMD in HIV-positive patients was used, as well as an IMD incidence for the non-vaccinated population of 11.3/100 000.<sup>[3]</sup> The distribution of disease according to serogroup was as follows (data on file provided by KOL on panel): serogroup A 6%; serogroup B 11%; serogroup C 7%; serogroup W 62%; serogroup Y 13%; serogroup other (Z, X, NG) 1%.

For those receiving the MCV4 vaccine, the incidence of IMD was decreased by the efficacy of the vaccine (80%).<sup>[9]</sup> Only 88% of the incidence was reduced by this 80% effectiveness, as only 88% of disease-causing serotypes were covered by the vaccine.

Long-term sequelae of IMD that were considered in the model included skin scarring, single and multiple amputation, mild and profound hearing loss and neurological disability. Direct costs as well as productivity loss costs were considered for long-term sequelae.

Owing to low vaccination coverage of the total SA population, herd effects were not considered in the base case.

As patients included in this model were HIV-positive and on treatment, those without IMD would already incur a disutility in the no-disease state as a result of being HIV-positive (age-weighted utility of 0.79 for no-disease state).<sup>[10]</sup> No data were found to indicate the disutility for those with IMD without long-term sequelae. Therefore, the utility of 79% for HIV-positive patients on treatment was used. For those with long-term sequelae, an additional disutility of 28% in those <18 years, and 27% in those ≥18 years, was used to calculate the age-weighted utility for those with long-term sequelae as 51%.<sup>[11]</sup>

## Costs

Costs considered in the model included direct medical costs, such as vaccination cost, cost of treating the disease and cost of treating sequelae of the disease, as well as indirect costs such as loss of productivity attributed to the disease and to its long-term sequelae.

The vaccinated population received the cost of two primary doses of vaccine at model entry, as well as 25% of one-fifth of the booster cost. To account for booster vaccination after 5 years, because it is given at model entry, the model assumes the cost of the booster vaccine is reduced by 20% (mortality due to disease), so only 80% of the booster cost is applied. The vaccination price used in the model was ZAR630.39 per dose. An additional vaccination administration fee of ZAR189.00 was added.

Micro-costing was used to determine the cost of treating IMD. The elements costed were gathered from the Delphi panellists, and costs were attributed to each item from the Add wording for Uniform Patient Fee Schedule (UPFS) schedule.<sup>[12]</sup> Meningococcal treatment guidelines for SA were used to estimate the medicine items to cost, as well as the diagnostic and laboratory tests.

The costs associated with each long-term sequelae event were also calculated using micro-costing, where the resource use for out-of-hospital GP and specialist visits, as well as resource use (number of days spent) in ICU, high care and general ward were gathered from Delphi panellists. Costs were gathered from the UPFS. Only first-year costs were allocated in the cycle where the long-term sequelae were diagnosed. No direct costs, in the years following diagnoses, were allocated. Due to a lack of data for medication, laboratory tests and diagnostic tests used for each long-term sequelae event, these were not included in the micro-costing calculation. In the base case, a percentage was added to the total cost to account for medication, laboratory and diagnostic costs.

The total cost of treating a case of IMD was calculated at ZAR61 201. Table 1 shows the costs of treating different long-term sequelae associated with IMD.

Productivity loss costs were calculated for patients with long-term sequelae, as well as patients with long-term sequelae related to IMD (split between skin scarring, single amputation, multiple amputation, hearing loss and neurological disability).

The number of work-loss days for a patient with IMD is 33 days (12 days in hospital and 21 days booked off sick after discharge). This was estimated from Delphi panel consensus. An IMD patient will lose 50% of work years as a result of the disease.<sup>[13]</sup> An average age of 33 years, up to 65 years at retirement age, was used in the model. This indicates that a total of 16 years of work-loss is used in the model for an adult for the following major long-term sequelae events:<sup>[13]</sup>

- multiple amputation
- profound hearing loss
- neurological disability.

To calculate the costs related to loss of productivity when an employee is sick due to disease and to long-term sequelae, the

**Table 1. Costs per case of treating long-term sequelae of IMD**

Variable	Cost (ZAR)
Skin scarring	36 043
Single amputation	57 125
Multiple amputations	163 299
Mild hearing loss	33 400
Profound hearing loss	114 567
Neurological disability	158 974

IMD = invasive meningococcal disease.

percentage of persons in the workforce in each age category, the average daily wage for that age category and the number of work-loss days for each disease, per age group, were required.

The number of people in the workforce by group, and the average monthly wage, were obtained electronically from a KOL at Statistics SA (N Roux, personal communication). As provided, these data were split according to whether private and public healthcare facilities were utilised. The percentage of people in the workforce per age group was subsequently calculated by dividing the number of persons by the total population in each age group, for the public sector. The percentage of persons in the workforce who are HIV-positive and using public sector healthcare was reduced by 7.9%, as per Levinsohn *et al.*,<sup>[14]</sup> indicating that HIV-positive persons were 7.9% more likely to be unemployed. If a percentage was <0% after this calculation, it was set to 0%.

The average daily wage per age group was calculated by dividing the average monthly wage by 30.5. The number of work-loss days for the disease was assumed to be the same as the number of days required for hospitalisation for the disease plus the additional work-loss days for recovery at home after discharge, as per the Delphi panel inputs.

To calculate the total costs due to productivity loss, the percentage of persons who either had the disease or had a certain long-term sequela event was multiplied by the percentage of persons in the workforce, the average daily wage and the number of work-loss days.

For single and multiple amputations, it was additionally multiplied by the percentage of persons who perform manual labour, as it was assumed that only manual labourers would experience total productivity loss due to amputations.

**Results**

**Number of events**

A cohort of 24 531 818 HIV-positive patients on ARV treatment were included in the model, over 85 years. Of these, 12 265 909 were vaccinated over the 85 years.

The numbers of patients who contracted IMD in the vaccinated and non-vaccinated cohorts are summarised in Table 2. This shows

**Table 2. Summary of number of events**

Variable	MCV4, n	No vaccine, n	Incremental, n
Patients with IMD, no sequelae	60 888	92 243	-31 355
Patients with IMD, long-term sequelae			
Skin scarring	5 563	8 425	2 863
Single amputation	2 863	4 337	-1 473
Multiple amputation	164	248	-84
Mild hearing loss	409	620	-210
Profound hearing loss	1 902	2 881	-979
Neurologic disability	4 315	6 536	-2 221
Deaths due to IMD	3 458	5 238	-1 780
Total	79 562	120 527	-40 966

IMD = invasive meningococcal disease; MCV4 = meningococcal conjugate vaccine.

that by using the MCV4 vaccination, 39 185 IMD cases could be avoided (31 355 with no sequelae, and 7 830 with long-term sequelae). Over 85 years, by vaccinating with MCV4, 1 780 deaths due to disease could be avoided.

**Costs**

Total direct and indirect discounted costs are summarised in Table 3.

**Cost-effectiveness**

The discounted number of life years, quality-adjusted life years (QALY), total cost, incremental cost per life-year gained and incremental cost per QALY gained are shown in Table 4.

**Sensitivity analysis**

The results of the sensitivity analysis indicate that the model is most sensitive to the price and efficacy of the vaccine, the incidence of IMD, the case fatality rate of IMD and the percentage IMD caused by serogroup B (Fig. 1). Further reducing the vaccine price to ZAR314.00 (by approximately 50%, according to a price more likely to be used in the public sector) resulted in an incremental cost-effectiveness ratio (ICER) per QALY of ZAR356 674 (approximately 42% reduction in ICER per QALY).

**Discussion**

The public health results indicate that by vaccinating 50% of HIV-positive patients on ARV treatment over 85 years, 31 355 cases of IMD (without sequelae) can be avoided in that population. By vaccinating the same proportion of patients, 1 780 disease-related deaths, and 40 966 events in total (disease cases, long-term sequelae and deaths), can be avoided. This amounts to an average of 367 cases of IMD (without sequelae), 92 cases of IMD (with long-term sequelae) and 21 deaths avoided per year.

Cost results indicate (over 85 years) that there is an ~ZAR47.6 million reduction in indirect costs, but an increase in total cost of ~ZAR4.485 billion (due to vaccination costs) in the vaccination

**Table 3. Discounted direct and indirect costs**

Variable	MCV4, ZAR	No vaccine, ZAR	Incremental, ZAR
Direct	5 847 981 857	1 315 142 005	4 532 839 852
Indirect	141 490 587	189 144 542	-47 653 955
Total discounted	5 989 472 445	1 504 286 548	4 485 185 897

MCV4 = meningococcal conjugate vaccine.

**Table 4. Discounted cost-effectiveness results**

Variable	MCV4	No vaccine	Incremental
Life years, n	152 863 775	152 860 468	3 307
QALY, n	119 986 188	119 978 881	7 307
Total cost, ZAR	5 989 472 445	1 504 286 548	4 485 185 897
Incremental cost per life year gained, ZAR	-	-	1 356 239
Incremental cost per QALY gained, ZAR	-	-	613 805

QALY = quality-adjusted life year; MCV4 = meningococcal conjugate vaccine.

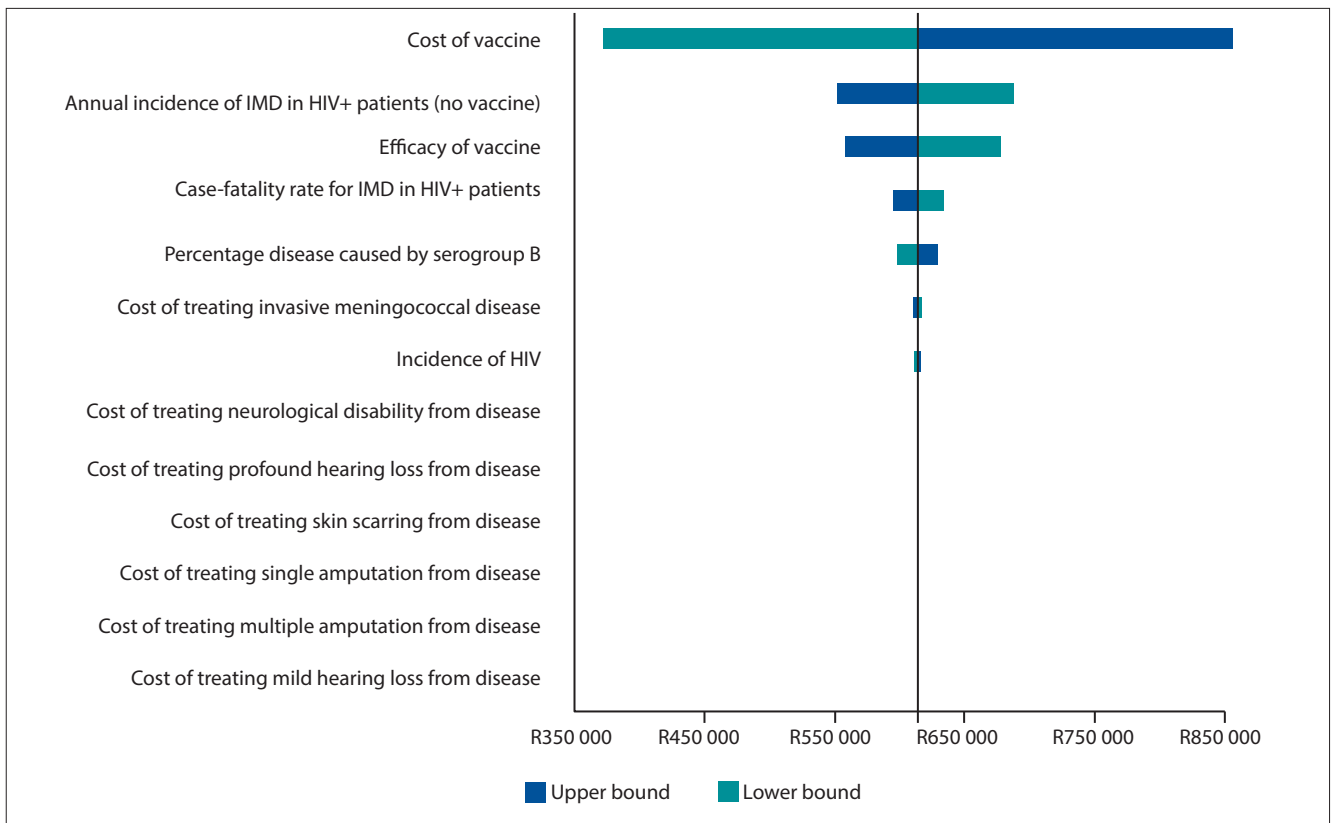


Fig. 1. Tornado diagram of sensitivity analyses performed. (IMD = invasive meningococcal disease).

compared with the no-vaccination arm. The costs of treating IMD with and without long-term sequelae are lower in the vaccination arm. This results in a base case ICER per QALY of ZAR613 805.

Sensitive inputs into the model include the price of the vaccine, the efficacy of the vaccine and the annual incidence of IMD in HIV-positive patients (when not vaccinated).

Preliminary results from a modelling study presented at the Advisory Committee on Immunization Practices in 2016 meeting indicated a cost per QALY gained of USD732 000 for HIV-positive persons in the USA, vaccinated with a primary series of MenACWY, followed by lifelong one-dose boosters every 5 years. The model was sensitive to the number of disease cases, deaths and vaccination costs.<sup>[15]</sup>

In contrast to this, studies performed in infant and adolescent populations indicated decreased costs to realise QALY gains. A cost-effectiveness analysis performed in Canada compared three scenarios: vaccination of 1-year-olds with serogroup C meningococcal conjugate vaccine (MCV-C) (reference scenario); vaccination with MCV-C at 1 and 12 years of age (scenario 2); and vaccination of 1-year-olds with MCV-C and 12-year-olds with MCV4 (scenario 3).<sup>[16]</sup> Using MCV4 instead of MCV-C in 12-year-olds resulted in an ICER per QALY gained of CAD30 978 (in 2004) compared with MCV-C at 1 year. Comparing scenario 3 with scenario 2 resulted in an ICER per QALY gained of CAD113 206. The difference in price between the two vaccines, and the efficacy of the MCV-C vaccination at 12 months, had the strongest impact on the cost/QALY in sensitivity analyses.

A more recent cost-effectiveness analysis performed in Canada found that MCV-C vaccination in infants and MCV4 vaccination in adolescents was dominant when compared with MCV-C vaccination in infants and adolescents.<sup>[11]</sup> Comparing MCV4 vaccination in infants and MCV4 vaccination in adolescents with MCV-C vaccination in infants and MCV4 vaccination in adolescents resulted in an ICER per QALY gained of CAD111 286. This can be considered cost-effective.

A cost-effectiveness analysis performed in the Netherlands found that vaccination with the MenACWY vaccine in 14-month-olds was cost-saving compared with vaccination with MenC.<sup>[17]</sup> Vaccination with MenACWY at 14 months and at 12 years resulted in the prevention of 7 additional cases of meningococcal disease over 99 years, compared with a single vaccination with MenC at 14 months, with an ICER per QALY gained of EUR635 334 (not considered to be cost-effective). When considering a scenario where serogroup-C disease incidence returns to pre-vaccination levels (owing to a loss of vaccine-induced herd immunity), vaccination with MenACWY at 14 months and 12 years was found to be potentially cost-effective.

In the USA, modelling a catch-up vaccination programme with MCV4 for persons aged 11 - 17 years, followed by routine vaccination of children 11 years of age in the following 9 years, averted 156 cases of meningococcal disease per year (direct effects).<sup>[18]</sup> When considering herd immunity, the number of cases averted per year increased to 825. The programme cost

approximately USD223 000 per case averted, USD2.6 million per death prevented, USD127 000 per life year gained and USD88 000 per QALY gained.

An older modelling study performed in the USA found that routine vaccination of 11-year-olds with MCV4 prevented 270 meningococcal disease cases and 36 deaths over 22 years, compared with no vaccination.<sup>[18]</sup> The cost per case averted was USD633 000, the cost per death averted was USD4 957 000, the cost per life year gained was USD121 000, while the cost per QALY gained was USD138 000. In sensitivity analysis, disease incidence, case fatality ratio and cost per vaccination were found to be the main factors affecting these results.

## Conclusion

Given the unique population dynamics in SA, and the fact that the present study is aimed at HIV-positive patients on ARV treatment, direct comparison of the study with previous studies is not possible.

While the results clearly illustrate the public health benefit of MCV4 in this risk population, conventional wisdom might dictate that it is not deemed a cost-effective intervention. Understanding the cyclical nature of the disease, the cost-effectiveness outcome of this model could change in the case of an outbreak or increased disease incidence. The dynamic inputs of this model would allow for review of the cost-effectiveness in such scenarios.

**Acknowledgements.** The authors would like to acknowledge the individuals who participated on the Delphi panel, and thank the panellists for their contributions.

**Author contributions.** The authors from TCD Outcomes Research (MdeN and JCdeB) performed the economic analysis, including study design, modelling, data collection, analysis and writing of the manuscript. TM provided funding for the study, and was part of the decision to publish and reviewed the manuscript.

**Funding.** While the study was sponsored by Sanofi Pty (Ltd), it had no additional role in the study design, data collection and analysis. The funder was involved in the decision to publish, and reviewed the manuscript after finalisation. The specific roles of the authors listed are described above. TCD Outcomes Research was the appointed external service provider to perform the economic analysis, including study design, modelling, data collection, analysis and writing of the manuscript.

**Conflicts of interest.** None.

- National Institute for Communicable Diseases. GERM South Africa Annual Report Pretoria: NICD, 2017. <http://www.nicd.ac.za/index.php/publications/germs-annual-reports/> (accessed 21 January 2019).
- Cohen C, Singh E, Wu HM, et al. Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. *AIDS* 2010;24(9):1351-1360. <https://doi.org/10.1097/QAD.0b013e32833a2520>
- Miller L, Arakaki L, Ramautar A, et al. Elevated risk for invasive meningococcal disease among persons with HIV. *Ann Intern Med* 2014;160(1):30-37. <https://doi.org/10.7326/0003-4819-160-1-201401070-00731>
- Simmons RD, Kirwan P, Beebejaun K, et al. Risk of invasive meningococcal disease in children and adults with HIV in England: A population-based cohort study. *BMC Med* 2015;13:297. <https://doi.org/10.1186/s12916-015-0538-6>
- Meiring S, Hussey G, Jeena P, Parker S, von Gottberg A. Recommendations for the use of meningococcal vaccines in South Africa. *South Afr J Infect Dis* 2017;32(3):82-86. <https://doi.org/10.1080/23120053.2017.1359939>
- Dlamini SK, Madhi SA, Muloiswa R, et al. Guidelines for the vaccination of HIV-infected adolescents and adults in South Africa. *S Afr J HIV Med* 2018;19(1):a839. <https://doi.org/10.4102/sajhivmed.v19i1.839>
- English GM, Keran GL. The prediction of air travel and aircraft technology to the year 2000 using the Delphi method. *Transportation Research* 1976;10(1):1-8. [https://doi.org/10.1016/0041-1647\(76\)90094-0](https://doi.org/10.1016/0041-1647(76)90094-0)
- Macneil JR, Cohn AC, Zell ER, et al. Early estimate of the effectiveness of quadrivalent meningococcal conjugate vaccine. *Pediatr Infect Dis J* 2011;30(6):451-455. <https://doi.org/10.1097/INF.0b013e31820a8b3c>
- Cleary S, Boule A, McIntyre D, Coetzee D. Cost-effectiveness of antiretroviral treatment for HIV-positive adults in a South African township. [https://www.msf.org.za/system/tdf/final\\_report\\_HST.pdf?file=1&type=node&id=3228](https://www.msf.org.za/system/tdf/final_report_HST.pdf?file=1&type=node&id=3228) (accessed 21 January 2019).
- Delea TE, Weycker D, Atwood M, et al. Cost-effectiveness of alternate strategies for childhood immunisation against meningococcal disease with monovalent and quadrivalent conjugate vaccines in Canada. *PLoSOne* 2017;12(5):e0175721. <https://doi.org/10.1371/journal.pone.0175721>
- National Department of Health, South Africa. Uniform patient fee schedule (UPFS) for paying patients attending public hospitals: April 2015. Pretoria: NDoH, 2015.
- Christensen H, Irving T, Koch J, et al. Epidemiological impact and cost-effectiveness of universal vaccination with Bexsero to reduce meningococcal group B disease in Germany. *Vaccine* 2016;34(29):3412-3419. <https://doi.org/10.1016/j.vaccine.2016.04.004>
- Levinsohn JA, McLaren Z, Shisana O, Zuma K. HIV status and labour market participation in South Africa. NBER Working Paper No. 16901. March 2011. JEL No. O12. <http://www.nber.org/papers/w16901.pdf> (accessed 21 January 2019).
- Ortega-Sanchez I. Cost-effectiveness of meningococcal vaccination in HIV-infected people in the US – preliminary. ACIP [Advisory Committee on Immunization Practices] meeting, June 2016. <http://www.nitag-resource.org/uploads/media/default/0001/03/fce42b199fb305ba053e5323b2cb705ecf5cc276.pdf> (accessed 21 January 2019).
- De Wals P, Coudeville L, Trottier P, Chevat C, Erickson LJ, Nguyen VH. Vaccinating adolescents against meningococcal disease in Canada: A cost-effectiveness analysis. *Vaccine* 2007;25(29):5433-5440. <https://doi.org/10.1016/j.vaccine.2007.04.071>
- Hepkema H, Pouwels KB, van der Ende A, Westra TA, Postma MJ. Meningococcal serogroup A, C, W<sub>135</sub> and Y conjugated vaccine: A cost-effectiveness analysis in the Netherlands. *PLoSOne* 2013;8(5):e65036. <https://doi.org/10.1371/journal.pone.0065036>
- Ortega-Sanchez IR, Meltzer MI, Shepard C, et al. Economics of an adolescent meningococcal conjugate vaccination catch-up campaign in the United States. *Clin Infect Dis* 2008;46(1):1-13. <https://doi.org/10.1086/524041>

1. Joint United Nations Programme on HIV/AIDS. Country South Africa Overview. Geneva: UNAIDS, 2019. <http://www.unaids.org/en/regionscountries/countries/southafrica> (accessed 21 January 2019).

Accepted 28 August 2019.