# Surveillance Optimization to Detect Poliovirus in the Pre-Eradication Era: a Modelling Study of England and Wales

| | |
|---|---|
| Journal: | *Epidemiology and Infection* |
| Manuscript ID | HYG-OM-10192-Feb-20.R1 |
| Manuscript Type: | Original Paper |
| Date Submitted by the Author: | n/a |
| Complete List of Authors: | O'Reilly, Kathleen; London School of Hygiene & Tropical Medicine, Epidemiology and Population Health<br>Grassly, N; Imperial College London<br>Allen, David; London School of Hygiene and Tropical Medicine, Pathogen Molecular Biology Department<br>Bannister-Tyrrell, M; AU Vet Med Library<br>Cameron, Angus; AU Vet Med Library<br>Carrion Martin, I; MSF<br>Ramsay, Mary; Health Protection Agency, Health Protection Agency<br>Pebody, Richard; Public Health England Colindale, Respiratory Diseases Department<br>Zambon, Maria; Public Health England |
| Keyword: | Polio, Surveillance, Surveillance system, Virology (human) and epidemiology |
| Abstract: | Surveillance for acute flaccid paralysis (AFP) cases is essential for polio eradication. However, as most poliovirus infections are asymptomatic and some regions of the world are inaccessible additional surveillance tools require development. Within England and Wales we demonstrate how inclusion of environmental sampling (ENV) improves the sensitivity of detecting either wild or vaccine derived polioviruses (VDPVs) when compared to current surveillance. Statistical modelling was used to estimate the spatial risk of wild and VDPV importation and circulation in England and Wales. We estimate the sensitivity of each surveillance mode to detect poliovirus and the probability of being free from poliovirus, defined as being below a pre-specified prevalence of infection. Poliovirus risk was higher within local authorities in Manchester, Birmingham, Bradford and London. The sensitivity of detecting wild poliovirus within a given month using AFP and enterovirus surveillance was estimated to be 0.096 (95% CI 0.055, 0.134). Inclusion of ENV in the 3 highest risk local authorities and a site in London increased surveillance sensitivity to 0.192 (95% CI 0.191 0.193). The sensitivity of ENV strategies can be compared using the framework by varying sites and the frequency of sampling. The probability of being free from poliovirus slowly increased from the date of the last case in 1993. ENV within areas thought to have the highest risk improves detection of poliovirus, and has the potential to improve confidence in the polio-free status of England and Wales and detect VDPVs. |
| | |

London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

# Surveillance Optimization to Detect Poliovirus in the Pre-Eradication Era: a Modelling Study of England and Wales

K. M. O'Reilly[1,2,3*], N. C. Grassly[3], D. J. Allen[4,5,6], M. Bannister-Tyrrell[7], A. Cameron[8], A. I. Carrion Martin[6,9], M. Ramsay[6], R. Pebody[6], M. Zambon[6]

[1] Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

[2] Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, UK

[3] MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, St Mary's Campus, Imperial College London, London, UK

[4] Department of Infection Biology, London School of Hygiene and Tropical Medicine, London, UK

[5] Vaccine Centre, London School of Hygiene & Tropical Medicine, London, UK

[6] National Infection Service, Public Health England, London, UK

[7] Ausvet Europe, 3 Rue Camille Jordan, 69001 Lyon, France

[8] Ausvet, 5 Shuffrey Street, Fremantle, WA 6160, Australia

[9] European Program for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control, (ECDC), Stockholm, Sweden.

* Corresponding author (kathleen.oreilly@lshtm.ac.uk)

Running head: Polio Surveillance in England and Wales

## Summary

Common to many European countries, England and Wales remain at risk of poliovirus importations and must continue to carry out surveillance in the pre-eradication era. Within England and Wales we demonstrate how inclusion of environmental sampling (ENV) improves the sensitivity of detecting either wild or vaccine derived polioviruses (VDPVs) when compared to current surveillance. Statistical modelling was used to estimate the spatial risk of wild and VDPV importation and circulation in England and Wales. We estimate the sensitivity of each surveillance mode to detect poliovirus and the probability of being free from poliovirus, defined as being below a pre-specified prevalence of infection. Poliovirus risk was higher within local authorities in Manchester, Birmingham, Bradford and London. The sensitivity of detecting wild poliovirus within a given month using acute flaccid paralysis~~AFP~~ and enterovirus surveillance was estimated to be 0.096 (95% CI 0.055~~7~~, 0.134~~0~~). Inclusion of ENV in the 3 highest risk local authorities and a site in London increased surveillance sensitivity to 0.~~270~~ 192 (95% CI 0.191~~239~~ 0.~~301~~193). The sensitivity of ENV strategies can be compared using the framework by varying sites and the frequency of sampling. ENV placed within areas of high risk improves detection of poliovirus, and makes best use of the intensive sampling technique required.

## Abstract

Surveillance for acute flaccid paralysis (AFP) cases is essential for polio eradication. However, as most poliovirus infections are asymptomatic and some regions of the world are inaccessible additional surveillance tools require development. Within England and Wales we demonstrate how inclusion of environmental sampling (ENV) improves the sensitivity of detecting either wild or vaccine derived polioviruses (VDPVs) when compared to current surveillance. Statistical modelling was used to estimate the spatial risk of wild and VDPV importation and circulation in England and Wales. We estimate the sensitivity of each surveillance mode to detect poliovirus and the probability of being free from poliovirus, defined as being below a pre-specified prevalence of infection. Poliovirus risk was higher within local authorities in Manchester, Birmingham, Bradford and London. The sensitivity of detecting wild poliovirus within a given month using AFP and enterovirus surveillance was estimated to be 0.096 (95% CI 0.0557, 0.1340). Inclusion of ENV in the 3 highest risk local authorities and a site in London increased surveillance sensitivity to 0.192270 (95% CI 0.191239 0.193301). The sensitivity of ENV strategies can be compared using the framework by varying sites and the frequency of sampling. The probability of being free from poliovirus slowly increased from the date of the last case in 1993 ~~and illustrated the added value of enhanced enterovirus surveillance in the 1990s~~. ENV within areas thought to have the highest risk improves detection of poliovirus, and has the potential to improve confidence in the polio-free status of England and Wales and detect VDPVs.




London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

## Introduction

Indigenous wild poliovirus has been not been reported within England and Wales since the 1970s [1]. The elimination of poliomyelitis was achieved largely through vaccination of children and adults, using both the oral and inactivated polio vaccines (OPV and IPV, respectively). The IPV was introduced in 1956 and was replaced by the OPV in 1962 where it was part of the routine immunisation programme. In 20041988 the OPV was replaced by the IPV owing to the lower risk of vaccine-associated paralytic poliomyelitis (VAPP) cases. After the introduction of vaccination wild poliomyelitis cases quickly reduced in number; although sporadic imported cases of wild poliomyelitis cases have been reported within England and Wales until the 1980s, emphasising the need for high immunisation rates until polio is eradicated globally [2].

Across the decades from endemicity to elimination within England and Wales, surveillance for poliomyelitis has required adaptation. Global surveillance for poliomyelitis was developed in the 1990s within the Pan American Health Organization to detect cases, focussed within polio endemic settings. All cases of acute flaccid paralysis (AFP, the typical clinical presentation of poliomyelitis) in children <15 years should be investigated, and country surveillance rates have been used to determine an adequate surveillance system. AFP surveillance was instituted throughout the United Kingdom by 1991 where children <16 years of age presenting with AFP of any aetiology were investigated for poliomyelitis [1]. The reported AFP rate was ~0.38 per 100,000 and ~54% of cases had at least 1 stool sample collected for virology. Approximately 58% of AFP cases were discarded as polio and diagnosed as Guillain-

Barre syndrome. The comparatively low AFP reporting rate has been consistent in subsequent years and reflects reporting rates within other high-income countries in Western Europe [3]. To further support the evidence base for the polio-free status of England and Wales, enterovirus surveillance (ENT) was included as part of the poliovirus submissions in the early 2000s, where children presenting with meningitis (a rarer clinical presentation of poliovirus) were tested for the presence of enterovirus infection, including poliovirus [1]. However, AFP and ENT surveillance will only detect clinical disease and as poliovirus infection is largely asymptomatic more appropriate tools are required. Internationally, environmental sampling (ENV) for poliovirus has been very useful in providing both evidence of elimination but also in detection of small outbreaks and otherwise undetected transmission in IPV vaccinated~~ion~~ populations (where IPV protects against poliomyelitis but provides little mucosal immunity against infection) [4].

As eradication draws closer, surveillance for residual transmission and early indications of new importations and emergence events becomes increasingly important [5]. Each WHO regional office is carrying out a certification process for poliomyelitis eradication, where epidemiological evidence is reviewed to ascertain the polio-free status of each country [3]. One challenge is to assess and compare the available evidence of being polio-free given the different epidemiological surveillance activities and importation risk within each country. Additionally, vaccine-derived polioviruses (VDPVs) have increased in incidence since the removal of serotype-2 from OPV in 2016. VDPVs originate from the OPV vaccine but have acquired specific mutations that increase the probability of poliovirus infection resulting in paralysis, and easily spreads in unvaccinated populations. Although no VDPVs have been detected

in England and Wales, it remains essential to have sufficient surveillance to detect any importation and transmission events.

We make the distinction between detection of wild poliovirus and vaccine-derived poliovirus (VDPVs) because wild infections now consist of only serotype 1, and a majority of VDPV infections are of serotype 2 with a lower probability of clinical disease. We assume that current surveillance activities continue and explore how introducing ENV surveillance can supplement current activities. Using a statistical framework we aim~~ed~~ to answer;

1. Where in England and Wales should ENV surveillance be implemented to optimise detection of wild-type and VDPVs?
2. How does ENV surveillance improve the evidence that England and Wales are free from wild-type and VDPVs?

# Methods

Poliomyelitis cases are classified according to virus origin; wild-type poliomyelitis cases are those that have a close genetic relation to other wild-type viruses whilst vaccine-associated poliomyelitis cases have originated from the attenuated strain used in the OPV. In this analysis we consider wild-type poliovirus, which now consist only of serotype 1, and VDPVs which we assume to be of serotype 2 [6]. We do not consider vaccine-associated paralytic poliomyelitis cases or transmission from immune-deficient VPDV shedders [7]. These considerations are in line with the England and Wales National Guidelines for Polio [8].

*Estimating the spatial variation in the potential for poliovirus circulation in England and Wales*

Poliovirus circulation is defined as the sustained circulation through several chains of transmission of either wild-type or VDPVs within a localised area of England and Wales as a result of importation of the index infection (or case). The potential for poliovirus circulation was assumed to be the combined effect of the importation rate and the probability of local virus circulation, and was estimated for each local authority (LA). We assume that poliovirus importation varies spatially within England and Wales according to localised international migration. Importation will be driven by international travel; either residents acquiring poliovirus while abroad or through the arrival of international visitors. While the numbers of residents travelling internationally and the number of visitors is well documented at a country level, the sub-national location of both of these groups is not adequately reported. We make a simplifying

assumption that the location of foreign-born nationals approximates the location of residents visiting countries and for visitors from each country. We focus on residents from countries that have reported either wild-type or VDPVs between 2015-2017 (Table 1).

Data on the locality of foreign-born nationals are available from census data [9]. These data are reported at a local authority (LA) level, consisting of 326 geographical units within England and 22 within Wales (348 in total). The travel patterns of UK residents and visitors to the UK are available from the International Passenger Survey (IPS) [10]. Only data for residents and visitors to Pakistan and India were available with sufficient accuracy, the remaining countries were grouped with other countries within a geographical region (West Africa, South East Asia, Middle East) and the numbers were adjusted according to the proportion of the region that reside in each country.

The probability of local poliovirus circulation (herein referred to as poliovirus circulation) was estimated. We assumed that for each LA the probability of circulation follows a binomial model with exposure being the number of movements between England and Wales and each country and the probability of circulation given introduction (supplement). Since 2004 the IPV vaccine was included in the routine immunisation schedule, as part of the 'pentavalent' vaccine, and the OPV was phased out. Circulation given introduction is a function of the assumed basic reproduction number and local pentavalent coverage ~~(which includes the inactivated polio vaccine)~~. For LAs estimated to have a higher poliovirus risk the relevant water company and, where possible, the likely sewage treatment works that would need to be sampled are provided.

*Estimating the probability of being free from poliovirus using surveillance data*

Being 'free' from poliovirus is a distinct concept from elimination or eradication. Elimination is defined as the reduction to zero of the incidence of a specified disease in a defined geographical area and eradication is the permanent global reduction to zero of the incidence of infection. Being free from poliovirus refers to the incidence of infection being below a pre-specified threshold, and the threshold is informed by globally accepted indicators of surveillance. Whilst elimination was confirmed in England and Wales in the 1970s, surveillance is required to detect the re-emergence of polio should it be re-introduced. Comparison of different modes and efforts of surveillance can be subjective, and so to quantify the quality of evidence from surveillance, we estimate the probability of freedom from poliovirus [10].

We follow methods that have largely been developed in animal health [11, 124]. The population is divided into LAs and the surveillance system is divided into its constituent modes of surveillance (Figure 1). We then determine a 'design prevalence', which is the prevalence of infection that the surveillance system is designed to detect. We use the standard surveillance indicator within polio eradication of 1 AFP case (all causes) per 100,000 individuals aged less than 15 years per year. As infection is likely to cluster (especially if an epidemic occurs), we include this by specifying the regional design prevalence of detecting at least 1 LA with poliovirus at the specified design prevalence. The combined effect of risk and design prevalence is included in the 'effective probability of infection' [12]. Each mode of surveillance (AFP, ENT and ENV) is then characterised by considering the sensitivity of detection at each stage of

sampling. Each is briefly described in turn below, and parameter values summarised in Table 2, and described in full in the supplement.

For AFP surveillance, the sensitivity is a product of the probability that an individual infected with poliovirus will develop symptoms consistent with AFP, which varies by serotype, the probability that an AFP case is admitted to a hospital and notified, and the probability that the case is correctly identified as poliomyelitis through collection and isolation of poliovirus in stool. This is summarised using the surveillance sensitivity per month ($CSe_{AFP}$).

ENT surveillance arises from investigation of individuals accessing healthcare ~~who are symptomatic~~ and from whom an enterovirus-positive specimen has been obtained. All NHS laboratories are requested to submit enterovirus-positive specimens for surveillance of poliovirus. ENT surveillance captures different clinical presentations, many of which are viral meningitis [13]. For infection with poliovirus, meningitis can occur in approximately 1% of clinical cases [14], with no available data on variation by serotype. In the model we assume the notification rate is as high as for presentation with AFP. A majority of clinical samples collected by ENT surveillance consist of either stool, which has good sensitivity to detect poliovirus [13], or cerebral spinal fluid samples where the sensitivity of detecting enteroviruses is lower. Between 2000-2011 in the UK clinical samples to detect enterovirus infections included 5032 cerebrospinal fluid samples and 2394 gastrointestinal samples (that are most likely stool samples) [15], where 43% of all enterovirus infections were detected via gastrointestinal samples. – PCR is usually carried out on clinical specimens which has been demonstrated to be a useful method in detection of enterovirus RNA in these sample

types [~~15~~16]. Where enterovirus RNA is detected, further laboratory investigations will aim to rule out poliovirus as the causative agent. To account for the variable sensitivity of cerebrospinal and stool samples the sensitivity of individual clinical samples is assumed to have a lower confidence bound when compared to AFP surveillance (where all clinical samples are stool). In the model the sensitivity of ENT surveillance over a period of one month is $CSe_{\mathrm{ENT}}$.

ENV surveillance is included in the framework by specifying whether each LA includes ENV. For those LAs with no ENV the sensitivity of ENV to detect poliovirus is zero. As ENV surveillance is under development in England and Wales we vary the frequency and location of ENV to explore the effect on surveillance sensitivity. The sensitivity of a sample is assumed to depend on the proportion of residents included in the sewage catchment, the probability that a sample contains poliovirus if an individual is shedding and the laboratory sensitivity which is thought to be high [17]. The sensitivity of AFP surveillance over a period of one month is $CSe_{ENV}$.

The combined surveillance sensitivity of the system is calculated; $\underline{CS}\sout{S}Se = 1 - (1 - CSe_{AFP})(1 - CSe_{ENT})(1 - CSe_{ENV})$. Using the principal of the negative predictive value of a test, the probability of being infection free within a given month can be calculated. The probability of being polio free was then estimated for each month from January 1993 to present day, with the addition of ENT surveillance in 1997, and assuming ENV in 2019. All the analysis was carried out in the software R (version 3.6.1.) and the code to replicate the analysis is available (https://github.com/kath-o-reilly/polio-FFI-UK).

# Results

*Spatial estimates of poliovirus risk in England and Wales*

Between 2015 and 2017 Afghanistan, Pakistan and Nigeria reported cases of wild-type poliomyelitis while Pakistan, Nigeria, Madagascar, Laos, DR Congo, Syria, Guinea and Myanmar reported cases of VDPVs. Within Pakistan and Nigeria, more visits were made by residents of England and Wales to the country than visitors from each country (Table 1). For Afghanistan, Pakistan and Nigeria a majority of visitors were visiting friends and relatives, supporting the assumption that their location will correlate with the location of foreign-born nationals.

Within England and Wales the locality of long and short term residents born outside of England and Wales varies spatially and are often focussed within cities and associated conurbations, especially Birmingham, Bradford, London, and Manchester. Coverage of the pentavalent vaccine varies across England and Wales, with an average of 96.3% per LA (supplement). The LAs where foreign-born nationals are frequently located are often correlated with areas that report low pentavalent coverage. When combining these data together to estimate the probability of poliovirus circulation 21 LAs comprise of over 50% of the estimated risk and several of these LAs are located within cities including Manchester, Birmingham and Greater London (Figure 2 and Table 3). Consequently, if ENV sampling were targeted within catchment areas that cover these LAs, this would be an efficient form of targeted surveillance.

*Estimating the probability of being poliovirus free from surveillance data*

Detection of poliovirus through clinical surveillance – which is implemented in England and Wales - is low as clinical disease is a minority of infections. The probability of detecting one infection from clinical surveillance (the combined use of AFP and ENT surveillance) is estimated to be 0.0032~~45~~ (95% CI 0.0017~~783~~ 0.0048~~179~~) for wild-type poliovirus and 0.0003~~3669~~ (95% CI 0.0001~~6075~~ 0.000641) for VDPVs. The freedom from infection model uses these values along with~~with~~ estimates of ~~the risk of~~ poliovirus circulation within each LAs to estimate the sensitivity of each mode of surveillance per month. Using the information available on sampling sensitivity and surveillance activities within England and Wales, the sensitivity of detecting wild-type poliovirus using AFP and ENT surveillance at the specified design prevalence within a given month was estimated to be 0.096 (95% CI 0.05~~57~~ 0.13~~40~~), and lower for VDPV (0.011~~120~~ with 95% CI 0.005~~38~~ 0.0210).

We explore several scenarios for the use of ENV in England and Wales. ENV surveillance has a differing profile to clinical surveillance as it is highly sensitive where it is implemented but is limited by the size of the sewage catchment area included in sampling. Implementing monthly ENV in Birmingham, Manchester and Bradford (the LAs with highest risk of importation and circulation, strategy A (Table 3)) the sensitivity of ENV ($CSe_{ENV}$) is estimated to be 0.0868 (95% CI 0.0867, 0.0869). Sampling in the three high risk sites and Beckton (strategy B~~London~~) has an estimated sensitivity of 0.192 (95% CI 0.191, 0.193). Performing fortnightly instead of monthly sampling in the same sites would result in only a moderate increase in sensitivity despite a doubling of samples. ENV surveillance capturing LAs that comprise 50% of the total risk (strategy C) would correspond to an estimated sensitivity of 0.32 (95% CI 0.31, 0.33),

and would consist of 10 ENV samples per month. Including monthly ENV surveillance within Birmingham, Manchester and Bradford would increase the total sensitivity of detecting wild-type poliovirus to 0.174 (95% CI 0.139 0.209) and with the addition of Beckton (London) the sensitivity would increase to 0.270 (95% CI 0.239 0.301), with slightly lower values for VDPV surveillance.

We then estimate ~~of~~ the probability that England and Wales was free from wild-type poliovirus, given the operating surveillance and the absence of cases or infections, from 1993 to present day. The probability of being poliovirus free increases over time from the date of the last reported case of poliomyelitis in England and Wales in 1993. The introduction of ENT surveillance in 1997 was estimated to moderately improve the rate of increase in the probability of being free from poliovirus due to the higher sensitivity (Figure 3). There was no noticeable difference in the temporal change in probabilities when different importation risks were assumed or when using the population movements from IPS data versus assuming a constant importation rate. Inclusion of ENV into the estimates for the latter years would not change the estimates of England and Wales being polio free, largely because the estimates are already above 99.9%. A comparison of VDPV is also shown, but it is noted that VDPVs have never been reported in England and Wales. The lower sensitivity of surveillance means that the probability of being infection free increases but at a lower rate. Inclusion of ENV in surveillance improves sensitivity to detect VDPVs, meaning that surveillance will also improve detection of introduced VDPVs.

## Discussion

In the final stages of polio eradication, surveillance for circulation of polioviruses remains essential. The practicalities of surveillance are becoming increasingly challenging owing to the reduced incidence of disease, an increase in the variety of risks that need to be considered and an increasingly connected world that potentially increases risk through population movement. The findings presented here illustrate the potential weaknesses of using clinical surveillance alone to detect poliovirus in England and Wales, and the added benefits of incorporating ENV. Using ENV in an informed, targeted manner has the potential to greatly enhance surveillance for polioviruses, thus expedite detection of importation events.

The approach described here assumes that spatial variation in risk within England and Wales can be quantified using data and used to inform where ENV should be targeted to maximise detection. ~~To the authors knowledge this is the first attempt to quantify the spatial variation in poliovirus risk within a polio-free setting.~~ Use of spatial risk mapping helps prioritize ENV sampling according to risk and estimation of surveillance sensitivity enable comparison of sampling strategies. This has been especially useful in developing the poliovirus environmental sampling strategy within England and Wales. Sampling sewage from the highest risk LAs targets surveillance within areas most likely to be exposed to poliovirus, and sampling within a large London sewage treatment works is advantageous as it covers a considerable proportion of the population with just one ENV sample. Within a pilot scheme implemented between 2016-2017 Sabin poliovirus was detected in several samples, illustrating that poliovirus can be detected within a large sewage plant [~~16~~17]. Sampling in more sites

largely out-performs more frequent sampling in the same sites, but may be sensitive to our assumptions on the duration of poliovirus shedding.

Much of the spatial variation in risk is due to movements between England and Wales and countries that have or are currently reporting wild-type and VDPV poliomyelitis cases. We assume that migration at a LA level is similar to the location of foreign-born nationals within the census. Data from IPS supports this assumption, as most residents report visiting friends and family when visiting Afghanistan, Pakistan and Nigeria. There are less data to quantify movements from Laos, DR Congo, Guinea, Myanmar and Syria, which have all reported poliomyelitis cases in recent years. With the emergence of VDPVs in Africa the risk of importation is likely to have only increased marginally due to the low number of movements between here and England and Wales. Should the incidence of VDPVs increase in Asia (and especially Pakistan which has both ongoing wild-type and VDPV transmission, and much more travel to England and Wales) the risk of importation into the ~~UK~~ England and Wales will further increase ~~due to many more movements between the UK and Asia~~. As VDPVs have a lower symptomatic rate the addition of ENV to clinical surveillance becomes even more important. Vaccination coverage within LAs influences the likelihood of virus circulation, and ensuring that coverage remains above 90% across communities remains essential. It is therefore a concern that some LAs, especially in London boroughs, consistently report coverage below this value and these are often the same LAs with a higher proportion of foreign-born residents. Risk factors associated with low pentavalent coverage have not been specifically explored in England and Wales, but studies for other vaccines suggest that ethnicity and socio-economic factors are

associated with lower coverage [~~17~~18]. Strategies to improve vaccination rates within these underserved communities should therefore be prioritised.

Estimates of the probability of being infection free are moderately sensitive to assumptions on the probability of importation, which remain uncertain within England and Wales. Visitors to countries that are at risk of poliovirus are recommended to receive a booster of IPV/pentavalent vaccine, and visitors from at-risk countries are required to provide evidence of recent vaccination history as part of the continued Public Health Emergency of International Concern for poliomyelitis. Visitors to Saudi Arabia, as part of religious pilgrimages (Hajj or Umrah) are recommended to receive vaccinations [~~18~~19]. Consequently, substantial efforts are put in place to reduce the risk of poliovirus importations to England and Wales, but the risk remains, as illustrated by recent importation events within other high income countries [~~19~~20, ~~20~~21].

There are several caveats to the analysis that may warrant further research. We have not considered the risks associated with laboratory release, which are currently considered low, but the relative risks associated with Polio Essential Facilities located in England and Wales will increase as polio eradication approaches the post-certification phase [~~21~~22]. We do not consider the risks associated with transmission of polioviruses from immune-compromised individuals shedding iVDPVs; despite intensive study there has only been a small handful of transmission events recorded and there is only one reported individual within the UK known to shed iVDPV [~~22~~23]. Further exploration of ENT surveillance for detecting polioviruses is warranted, as current stool sampling is limited even though the sensitivity of detection is high and the sampling is non-invasive. Populations of unvaccinated adults may pose a risk

within specific geographical communities but currently there is little information to rely on. Further details of catchment areas will be needed to select suitable sampling sites and this requires collaboration with water companies. Additionally, the precise sensitivity of an ENV sample is dependent on many factors not considered in the model but described elsewhere [~~23~~24]. Instead, we included a large range of uncertainty and took this decision because of the lack of data to inform calculations but this can be revisited should the data become available. The specified design prevalence affects the estimates of sensitivity and as eradication approaches a more stringent design prevalence may be warranted. Methodological developments may be required to validate the approach, such as simulation. With these caveats in mind, it should be noted that the exact risk probabilities may be uncertain but the relative difference between LAs and mode of surveillance should still hold.

## Conclusion

Surveillance for poliovirus is becoming increasingly complex owning to the different modes of surveillance, and the changing risk of poliomyelitis. This research ~~is the first~~ attempts to quantify the variation in poliovirus risk in a disease-free setting, and use of these estimates to compare different modes of surveillance. ENV surveillance will improve the sensitivity of surveillance, thus supporting the certification phase of polio eradication.

**Financial support:** Funded by the Medical Research Council (MR/J014362/1) and Bill and Melinda Gates Foundation (OPP1191821). The funder had no role in the design, implementation or interpretation of the results.

**Acknowledgements:** The authors would like to thank the PHE convened Polio Working Group which commissioned this work, Chris Thompson from Thames Water who assisted with the guiding the modelling framework, Jonathon Cook from the Office of National Statistics for providing country-level data from the International Passenger Survey. Members of Vaccine Epidemiology Group at Imperial College London have helpfully provided constructive feedback in developing the research, along with fruitful discussions with Professor Paul Fine (LSHTM).

## References


1. Salisbury, D. M., Ramsay, M. E., White, J. M. & Brown, D. W. Polio eradication: surveillance implications for the United Kingdom. J. Infect. Dis. 1997; 175 Suppl 1, S156-159.
2. Joce, R., Wood, D., Brown, D. & Begg, N. Paralytic Poliomyelitis in England and Wales, 1985-91. Br. Med. J. 1992; 305, 79–82.
3. WHO. 32ND meeting of the European regional commission for certification of poliomyelitis eradication (RCC). Available from: http://www.euro.who.int/en/health-topics/communicable-diseases/poliomyelitis/publications/2018/32nd-meeting-of-the-european-regional-commission-for-certification-of-poliomyelitis-eradication-rcc-report-2018
4. Manor, Y. *et al.* Intensified environmental surveillance supporting the response to wild poliovirus type 1 silent circulation in Israel, 2013. Eurosurveillance. 2014; 19, 1–10.
5. Asghar, H. *et al.* Environmental surveillance for polioviruses in the global polio eradication initiative. J. Infect. Dis. 2014; 210, S294–S303.
6. Burns, C. C., Diop, O. M., Sutter, R. W. & Kew, O. M. Vaccine-Derived Polioviruses. J. Infect. Dis. 2014; 210, S283-S293.
7. Macklin, G. *et al.* Prolonged Excretion of Poliovirus among Individuals with Primary Immunodeficiency Disorder: An Analysis of the World Health Organization Registry. Front. Immunol. 2017; 8, 1103.
8. PHE. National Guidelines for Clinical Management of Polio. (2019). Available from: https://www.gov.uk/government/collections/polio-guidance-data-and-analysis

9. 2011 Census - Office for National Statistics. https://www.ons.gov.uk/census/2011census.

10. ONS. International Passenger Survey. (2018). Available from: https://www.ons.gov.uk/surveys/informationforhouseholdsandindividuals/householdandindividualsurveys/internationalpassengersurvey

11. Martin, P. A. J., Cameron, A. R. & Greiner, M. Demonstrating freedom from disease using multiple complex data sources 1: a new methodology based on scenario trees. Prev. Vet. Med. 2007: 79, 71–97.

12. Cameron, A., Njeumi, F., Chibeu, D & Martin, T. Risk-based disease surveillance. Available from: http://www.fao.org/3/a-i4205e.pdf

13. Minor, P. D. & Muir, P. Enteroviruses. In: Zuckerman AJ, Banatvala JE, Pattison JR, Griffiths PD, Schoub BD, editors. in *Principles and practice of clinical virology* 467–490 (Wiley, 2004).

14. Mehndiratta, M. M., Mehndiratta, P. & Pande, R. Poliomyelitis. The Neurohospitalist 2014; 4, 223–229.

15. Kadambari S, Bukasa A, Okike IO, Pebody R, Brown D, Gallimore C, Xerry J, Sharland M, Ladhani SN. Enterovirus infections in England and Wales, 2000-2011: the impact of increased molecular diagnostics. Clin Microbiol Infect. 2014 Dec;20(12):1289-96. doi: 10.1111/1469-0691.12753.

~~15~~16. Iturriza-Gómara, M., Megson, B. & Gray, J. Molecular detection and characterization of human enteroviruses directly from clinical samples using RT-PCR and DNA sequencing. J. Med. Virol. 2006; 78, 243–253.

~~16~~17. Majumdar, M. *et al.* Isolation of Vaccine-Like Poliovirus Strains in Sewage Samples From the United Kingdom. J. Infect. Dis. 2018; 217, 1222–1230.

~~17~~18. Tiley, K. *et al.* What school-level and area-level factors influenced HPV and MenACWY vaccine coverage in England in 2016/2017? An ecological study. BMJ Open 2019; 9, e029087.

~~18~~19. PHE. Latest health and travel advice for Hajj and Umrah. Available from: https://www.gov.uk/government/news/latest-health-and-travel-advice-for-hajj-and-umrah

~~19~~20. Moran-Gilad, J., Kaliner, E., Gdalevich, M. & Grotto, I. Public health response to the silent reintroduction of wild poliovirus to Israel, 2013-2014. Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis. 2016; 22 Suppl 5, S140–S145.

2~~0~~. Yakovenko, M. L. *et al.* The 2010 outbreak of poliomyelitis in Tajikistan: epidemiology and lessons learnt. Euro Surveill. Bull. Eur. Sur Mal. Transm. Eur. Commun. Dis. Bull. 2014; 19, 20706.

~~21~~22. Wolff, C. *et al.* Progress toward laboratory containment of poliovirus after polio eradication. J. Infect. Dis. 2014; 210, S454–S458.

~~22~~.3. Dunn, G. *et al.* Twenty-Eight Years of Poliovirus Replication in an Immunodeficient Individual: Impact on the Global Polio Eradication Initiative. PLoS Pathog. 2015; 11, e1005114.

~~23~~24. Ranta, J., Hovi, T., Arjas, E. Poliovirus surveillance by examining sewage water specimens: studies on detection probability using simulation models. Risk Anal. 2001; 21, 1087–1096.

# Tables and Figures for "Surveillance Optimization to Detect Poliovirus in the Pre-Eradication Era: a Modelling Study of England and Wales"

***Table 1. Countries that have reported either wild of VDPVs between 2015-2017 and the reported number of movements between England and Wales.***

| Country | Population size (million) | Cases of wild poliovirus (2015-2017) | Incidence of wild poliovirus (2015-2017) (per million per year) | Cases of VDPVs (2015-2017) | Incidence of VDPVs (2015-2017) (per million per year) | Combined incidence | Travel to England and Wales (2016) | Visitors from England and Wales (2016) |
|---|---|---|---|---|---|---|---|---|
| **Afghanistan** | 34.6 | 47 | 0.45 | 0 | 0 | **0.45** | ND | 15,351 |
| **Pakistan** | 193.2 | 82 | 0.14 | 3 | 0.01 | **0.15** | 65,776 | 552,833 |
| **Nigeria** | 186 | 4 | 0.01 | 2 | 0 | 0.01 | 100,904 | 183,807 |
| **Madagascar** | 24.9 | 0 | 0 | 10 | 0.13 | 0.13 | ND | 8,289 |
| **Laos** | 6.8 | 0 | 0 | 11 | 0.54 | 0.54 | ND | 3,032 |
| **DRC** | 78.7 | 0 | 0 | 22 | 0.09 | 0.09 | ND | ND |
| **Syria** | 18.4 | 0 | 0 | 74 | 1.34 | 1.34 | ND | ND |
| **Guinea** | 12.1 | 0 | 0 | 7 | 0.19 | 0.19 | ND | ND |
| **Myanmar** | 52.9 | 0 | 0 | 2 | 0.01 | 0.01 | ND | 15,287 |

ND – no data, presumed to be very low

***Table 2. Estimates of surveillance probabilities used in the scenario tree analysis. The rationale behind the selected values are described in more detail in the Supplementary Material.***

| Surveillance | AFP | | ENT | | ENV | |
|---|---|---|---|---|---|---|
| **Model inputs** | | | | | | |
| | **Probability** | **Estimate (95% CI)** | **Probability** | **Estimate (95% CI)** | **Probability** | **Estimate (95% CI)** |
| Infection - wild | $Pr(case_{AFP})$ | 0.00531 (0.00412, 0.00668) | $Pr(case_{ENT})$ | 5.29e-05 (4.07e-05 6.74e-05) | Pr(shedding) | 0.80 |
| Infection - VDPV | | 0.000567 (0.000281, 0.000933) | | As above | | 0.80 |
| Notification | $Pr(notif_{AFP})$ | 0.9 (0.6, 0.99) | $Pr(notif_{ENT})$ | 0.9 (0.6, 0.99) | Pr(catchment) | varied |
| Sampling | $Pr(sample_{AFP})$ | 0.8 (0.5, 0.95) | $Pr(sample_{ENT})$ | 0.5 (0.1, 0.9) | Pr(sample) | 0.80 (0.5, 0.90)[1] |
| Test | $Pr(test_{AFP})$ | 0.97 (0.95, 1.00) | $Pr(test_{ENT})$ | 0.97 (0.95, 1.00) | $Pr(test_{ENV})$ | 0.97 (0.95, 1.00) |

[1] Monthly sampling

***Table 3. Summary of the Local Authorities that constitute over 50% of the estimated risk of poliovirus circulation in England and Wales.*** *The parentheses A, B, and C refer to the ENV sampling strategies described in the results.*

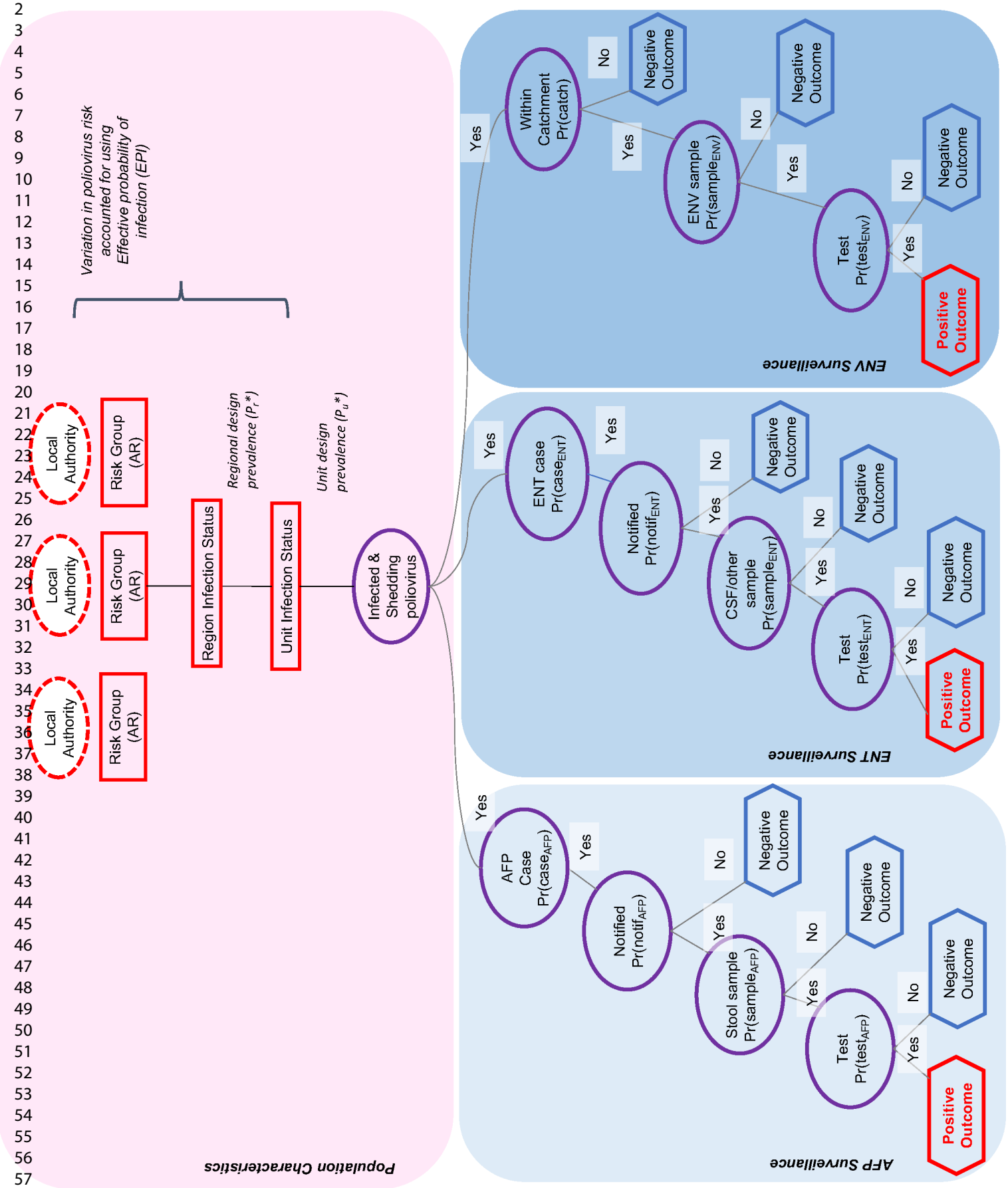
| Local Authority | County | Pentavalent Coverage[1] | Associated Water Company[2] | Pr(circulation) | % Total Estimated Risk | Population Size |
|---|---|---|---|---|---|---|
| Birmingham District (A) | West Midlands | 94.8* | Severn Trent - Minworth | 0.905 | 7.0% | 1,073,045 |
| Manchester District (A) | Greater Manchester | 95.9* | United Utilities - Davyhulme | 0.924 | 5.3% | 503,127 |
| Bradford District (A) | West Yorkshire | 97.2 | Yorkshire Water - Esholt | 0.947 | 4.6% | 522,452 |
| Newham (B) | London Borough | 94.2* | Thames Water - Beckton | 0.896 | 3.8% | 307,984 |
| Redbridge (B) | London Borough | 95.2* | Thames Water - Beckton | 0.912 | 2.6% | 278,970 |
| Ealing (C) | London Borough | 95.9* | Thames Water - Mogden | 0.923 | 2.4% | 338,449 |
| Leeds District (C) | West Yorkshire | 97.1 | Yorkshire Water - | 0.945 | 2.3% | 751,485 |
| Waltham Forest (B) | London Borough | 92.1* | Thames Water - Beckton | 0.864 | 2.2% | 258,249 |
| Luton (C) | Luton | 96.3 | Thames Water | 0.932 | 1.9% | 203,201 |
| City of Nottingham (C) | Nottingham | 94.7* | Severn Trent – Stoke Bardolph | 0.904 | 1.9% | 305,680 |
| Hounslow (C) | London Borough | 89.7* | Thames Water - Mogden | 0.830 | 1.9% | 253,957 |
| Brent (C) | London Borough | 93.1* | Thames Water - Mogden | 0.879 | 1.8% | 311,215 |
| Sheffield District (C) | South Yorkshire | 96.2 | Yorkshire Water | 0.929 | 1.5% | 552,698 |
| Slough (C) | Outer London | 94.5* | Thames Water | 0.901 | 1.5% | 140,205 |
| Hillingdon (C) | London Borough | 95.1* | Thames Water - Mogden | 0.911 | 1.5% | 273,936 |
| City of Westminster (B) | London Borough | 75.9* | Thames Water - Beckton | 0.675 | 1.4% | 219,396 |
| Caerdydd – Cardiff (C) | Wales | 95.0* | Glas Cymru | 0.909 | 1.4% | 346,090 |
| Kirklees District (C) | West Yorkshire | 98.1 | Yorkshire Water | 0.963 | 1.3% | 422,458 |
| Barnet (C) | London Borough | 92.1* | Thames Water - Mogden | 0.864 | 1.3% | 356,386 |
| Greenwich (C) | London Borough | 93.4* | Thames Water - Crossness | 0.883 | 1.2% | 254,557 |
| Barking and Dagenham (B) | London Borough | 90.5* | Thames Water - Beckton | 0.840 | 1.2% | 185,911 |

[1] Starred LAs indicate that the pentavalent coverage is below the national average. [2]Where possible the likely sewage treatment works is given.

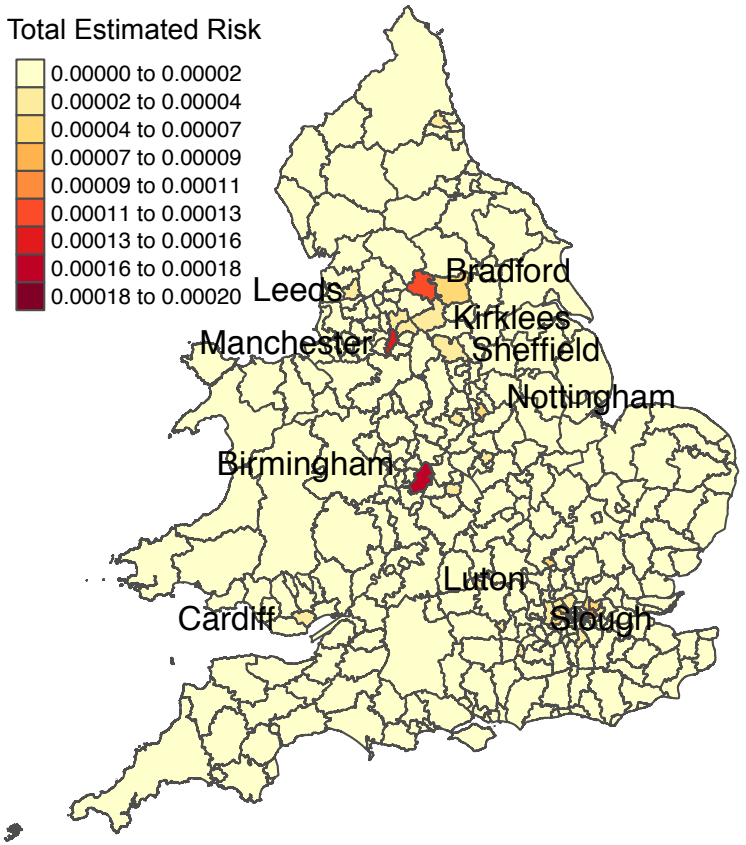
**Figure 1.** Scenario tree structure for acute flaccid paralysis (AFP), enterovirus (ENT) and environmental (ENV) surveillance in England and Wales. Dashed circles indicate category nodes, squares indicate infection nodes, circles indicate detection nodes and hexagons indicate outcome nodes.

**Figure 2.** Estimated risk of poliovirus circulation in local authorities within A) England and Wales, and B) London. C) The estimated risk within each local authority is ordered by reducing risk and compared to the cumulative percentage of the population to illustrate that 50% of estimated risk is focussed within <20% of the population.

**Figure 3.** Estimates of the probability of being poliovirus free within England and Wales. The dark brown line is the median estimate and the lighter brown lines are the 2.5 and 97.5 percentile estimates. The arrow indicates when enterovirus surveillance was introduced. The dashed line indicates a 0.95 probability, which was reached by early 1996 for the wild virus analysis (VDPV is shown as a comparator).

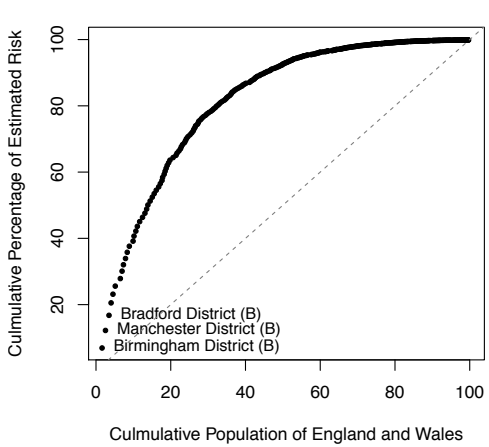

Population Characteristics
Local Authority
Risk Group (AR)
Local Authority
Risk Group (AR)
Local Authority
Risk Group (AR)
Region Infection Status
Unit Infection Status
Infected & Shedding poliovirus
Regional design prevalence ($P_r$*)
Unit design prevalence ($P_u$*)
Variation in poliovirus risk accounted for using Effective probability of infection (EPI)
AFP Surveillance
AFP Case Pr(case$_{AFP}$)
Notified Pr(notif$_{AFP}$)
Stool sample Pr(sample$_{AFP}$)
Test Pr(test$_{AFP}$)
ENT Surveillance
ENT case Pr(case$_{ENT}$)
Notified Pr(notif$_{ENT}$)
CSF/other sample Pr(sample$_{ENT}$)
Test Pr(test$_{ENT}$)
ENV Surveillance
Within Catchment Pr(catch)
ENV sample Pr(sample$_{ENV}$)
Test Pr(test$_{ENV}$)
Yes
No
Negative Outcome
Positive Outcome

A

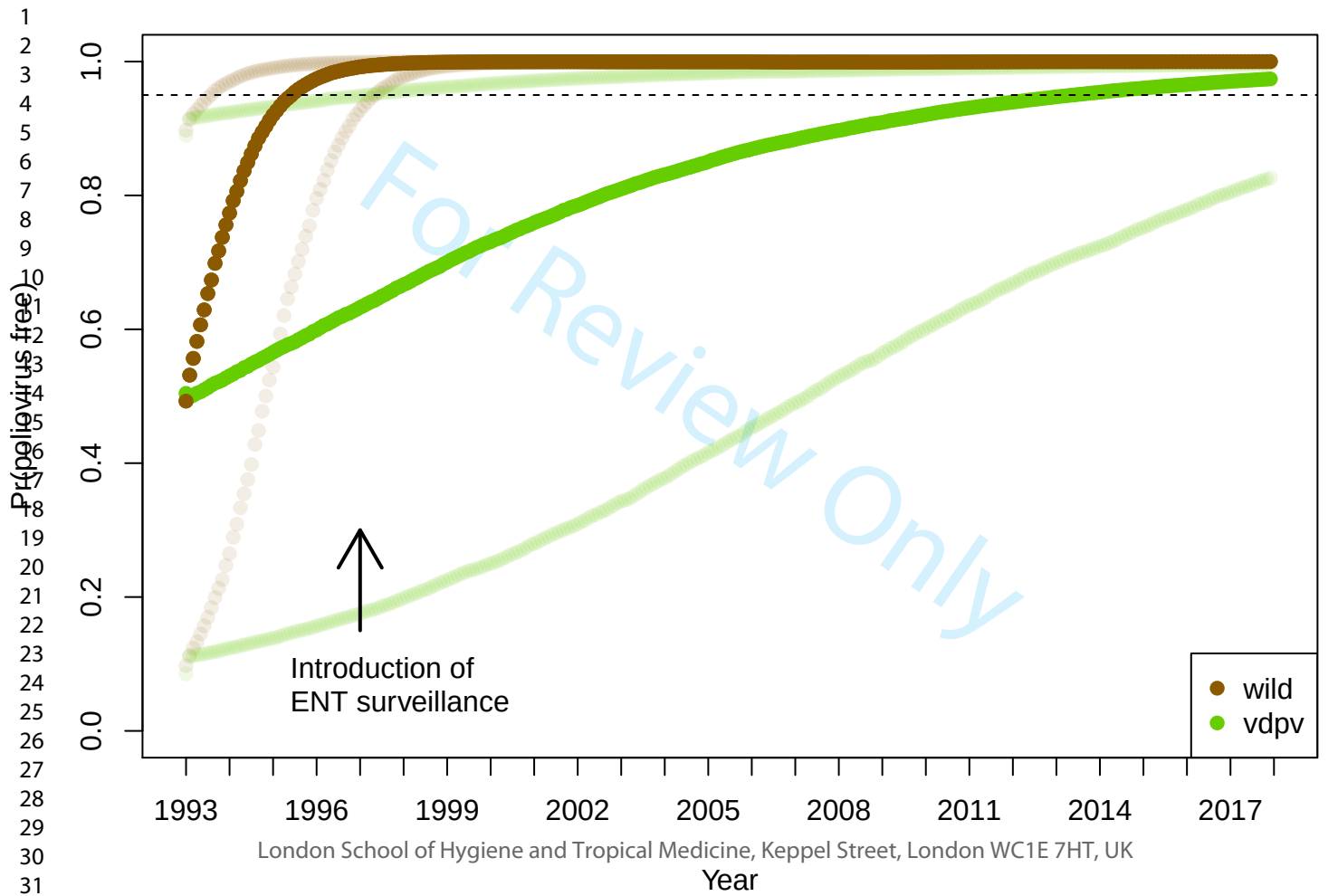



B


C



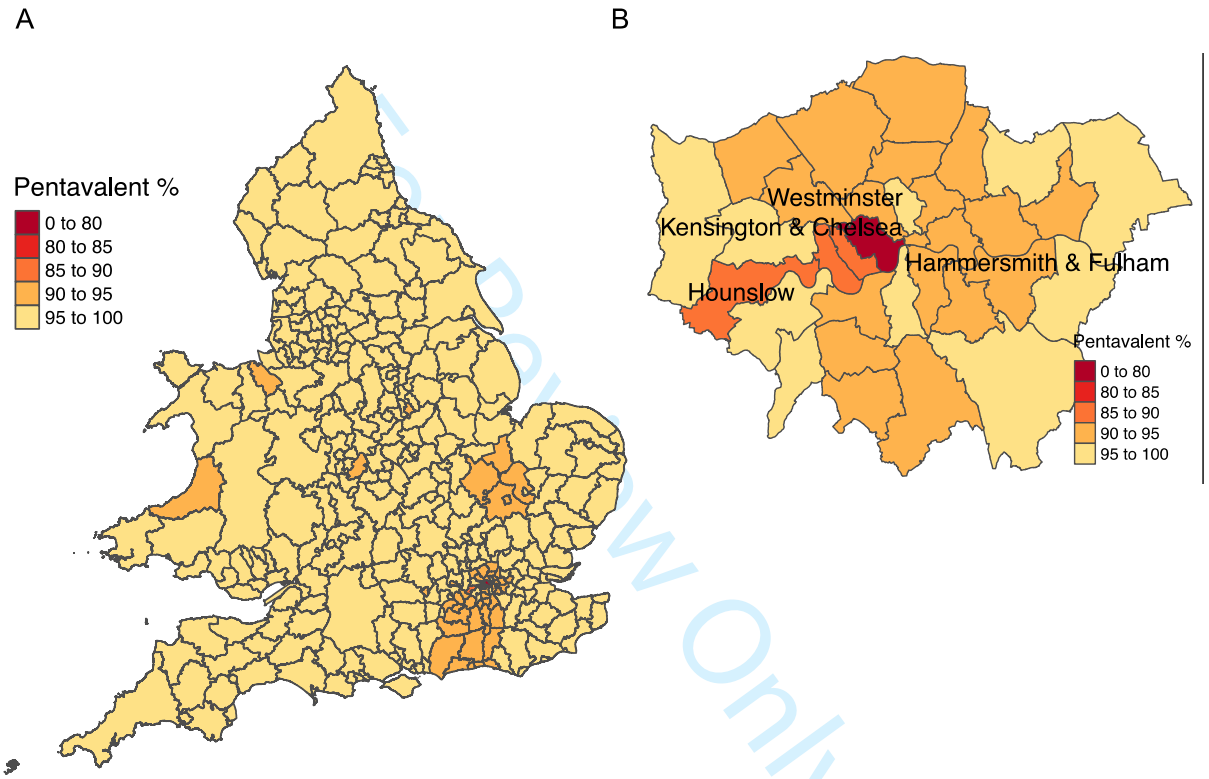

London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK


AFP & ENT surveillance
Pr(poliovirus free)
0.0
0.2
0.4
0.6
0.8
1.0
1993
1996
1999
2002
2005
2008
2011
2014
2017
Year
Introduction of
ENT surveillance
wild
vdpv
For Review Only
London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

# Supplementary Material for "Surveillance Optimization to Detect Poliovirus in the Pre-Eradication Era: a Modelling Study of England and Wales"

## 1. Vaccination coverage of the pentavalent vaccine

**Figure 1.** Average pentavalent coverage in children under 5 years of age by Local Authority within A) England and Wales and B) London Boroughs, 2011-2016. Local authorities that report coverage below 90% are highlighted.



## 2. Water companies and likely sewage treatment works serving high risk local authorities

***Severn Trent water company***

Severn Trent water company serves cities such as Birmingham, Nottingham, Leicester and Wolverhampton, as described on their website (https://www.severntrent.com/content/dam/stw-plc/water-resource-zones/WRMP-main-narrative.a.pdf). Minworth sewage treatment works (in Sutton Coldfield) serves the area of Birmingham City. The sewage treatment works of Stoke Bardolph is the likely treatment works that serves the Nottingham area.

***United Utilities***

The Greater Manchester area is served by United Utilities (https://www.unitedutilities.com/help-and-support/wastewater-services/). The treatment works that serves most of the Manchester are is the Davyhulme treatment works.

***Yorkshire Water***

Yorkshire water serves Bradford, with Esholt treatment works being the main sewage treatment for this area (https://www.yorkshirewater.com/waste-water-treatment-services/). For Leeds, the likely sewage treatment facility is Knostrop Wastewater Treatment Works. For Sheffield the likely sewage treatment works is Woodhouse Mill Sewage Treatment Works.

***Thames Water***

Thames water is the company that serves the Greater London area and some additional counties surrounding London. There are three main sewage treatment works; Beckton, Crossness and Mogden. The catchment of these treatment works has been well described by Thames Water (see figure), and can be used to approximate which would be sampled if carrying out surveillance of each population within the Local Authority.

***Glas Cymru***

Glas Cymru is the water treatment company for Wales. The likely sewage treatment works for Cardiff is Llwyn Onn Sewage Works.

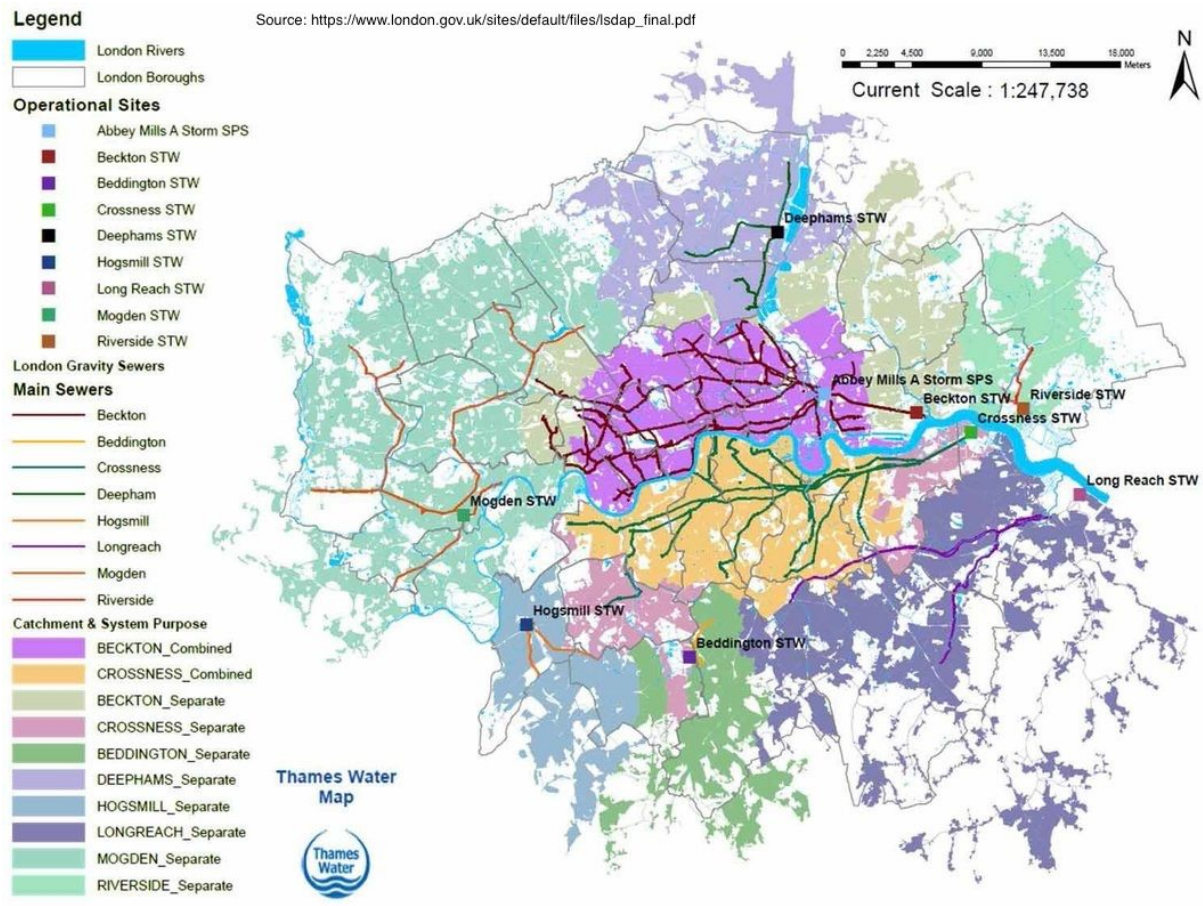



*Figure 2. Converging sewer network of Great London overlaid onto the London Boroughs (from Thames Water).*

### 3. Estimation of the spatial variation in the potential for poliovirus circulation in England and Wales

The probability of local poliovirus circulation (herein referred to as poliovirus circulation) is estimated. Within this context we are interested in circulation that may result in a poliomyelitis case. The basic reproduction number ($R_0$ - the average number of secondary cases from one infected person within a totally susceptible population) is useful measure of transmissibility of an infectious disease. When $R_0$ is greater than 1 the introduction of an infected individual may result in a large outbreak and if $R_0<1$ a large outbreak is unlikely. For vaccines with sterilizing immunity the probability of a major epidemic is given by $s=1-{}^{1}/_{(R_0(1-c))}$ where $c$ refers to the proportion of the population immunised. Rather than sterilising immunity, the IPV (which is part of the pentavalent vaccine) reduces the infectiousness and duration of infectiousness of immunised individuals,[1] so the probability of a major epidemic requires some adaptation; $s=1-{}^{1}/_{(R_0((1-c)+chd))}$ where $h$ is the relative infectiousness of immunised individuals and $d$ is the relative change in the duration of infectiousness.

The probability of major epidemic was estimated for each LA in England and Wales. To estimate the potential for poliovirus circulation the probability of circulation and the number of importation events ($M_j$) are combined assuming a binomial process. The risk for LA $i$ $\{i=1,...,N\}$ was estimated by summing over all locations considered to be a potential source ($j$);

$$R_i = 1 - \sum_{j=1}^{N} (1 - s_i)^{M_j}. \quad \text{equation 2.1}$$

For ENV surveillance in England and Wales to be optimised, sampling should be prioritised within sewage catchment areas with LAs with the highest risk. Wastewater treatment in England and Wales consists of eleven companies that manage regions similar to counties. Analysis of the spatial variation in poliovirus risk does not fully align with the location of sewage catchment areas but we provide an indication of the LAs and corresponding water company, and where possible the sewage treatment works that should be sampled to capture wastewater from each LA. The risk of poliovirus circulation is assumed to vary between wild and VDPVs based on just the location of reported cases and migration between England and Wales and these countries.

The estimated number of importations of either wild or VDPV poliovirus (*M*) is a function of the number of number of visitors to (N(i,j)) and from each country (N(j,i)), their vaccination status (v(i) and v(j)), and the incidence of WPV and VDPVs within each country.

$$M_{WPV}(\mathrm{j}) = \mathrm{N(i,j)}.I_{WPV}(\mathrm{j}).(1 - \mathrm{v(i)}) + \mathrm{N(j,i)}.I_{WPV}(\mathrm{j}).(1 - \mathrm{v(j)}) \quad \text{equation 2.2}$$

$$M_{VDPV}(\mathrm{j}) = \mathrm{N(i,j)}.I_{VDPV}(\mathrm{j}).(1 - \mathrm{v(i)}) + \mathrm{N(j,i)}.I_{VDPV}(\mathrm{j}).(1 - \mathrm{v(j)}) \quad \text{equation 2.3}$$

The total number of movements are $M_j = M_{WPV,j} + M_{VDPV,j}$.

## 4. Estimation of surveillance sensitivity

The methods for estimating the sensitivity of each mode of surveillance are first described.

For one poliovirus infection the sensitivity of detection through AFP surveillance ($SeU_{AFP}$) is estimated by taking the product of each step in the detection pathway (ie. from the probability of an infection being symptomatic through to the probability of the diagnostic test being positive, see Figure 1). If the risk of infection is constant across all locations, the estimate of sensitivity remains relatively simple. However, if the risk of infection varies across settings, it is intuitive that sampling within high risk settings would be preferable to sampling in low risk settings, and so the sensitivity needs to be adjusted. Acknowledging that this adjustment is an approximation,[2] we can use estimates of relative risks. The effective probability of infection (EPI) is used to account for variation in poliovirus risk across the LAs. The EPI combines the adjusted risk and the herd prevalence, $EPI_i = AR_i.P_h^*$ . The relative risks (RR), estimated in the previous section, and the proportion of the population (PrP) are used to calculate the adjusted risk (AR), by solving the simultaneous equations;

$$\frac{\mathrm{AR_i}}{\mathrm{AR_j}} = \frac{\mathrm{RR_i}}{\mathrm{RR_j}} \quad \text{equation 3.1}$$

$$\mathrm{AR_1.PrP_1} + \ldots + \mathrm{AR_n.PrP_n} = 1. \quad \text{equation 3.2}$$

High risk LAs will have an adjusted risk above 1.00 and consequently increased surveillance within these settings would have a more rapid improvement in the sensitivity of the entire

system. Combining these elements together, the sensitivity of detection through AFP surveillance is;

$$\mathrm{SeU}_{\mathrm{AFP,i}} = EPI_i.\Pr\left(\mathrm{case}_{\mathrm{AFP}}\right).\Pr\left(\mathrm{notification}_{\mathrm{AFP}}\right).\Pr\left(\mathrm{sample}_{\mathrm{AFP}}\right).\Pr(\mathrm{test}_{\mathrm{AFP}})$$

To calculate the sensitivity of AFP within each LA in a given month ($\mathrm{SSe}_{\mathrm{AFP,i}}$), we assume that all individuals (n) within each LA are included in surveillance;

$$\mathrm{CSe}_{\mathrm{AFP,i}} = 1 - (1 - \mathrm{SeU}_{\mathrm{AFP,i}})^{n_i}$$

Similar calculations are done for enterovirus ($\mathrm{CSe}_{\mathrm{ENT,i}}$) and environmental surveillance ($\mathrm{CSe}_{\mathrm{ENV,i}}$). All probabilities include uncertainty which is carried through the calculations and the mean and 95% credible intervals are given. See section 5 for a description of how estimates for each element of surveillance were derived.

We then want to estimate the sensitivity across the entire system for each mode of surveillance. First we need to combine estimates LAs for each surveillance system;

$$\mathrm{CSe}_{\mathrm{AFP}} = 1 - \prod_{i=1}^{M} CSe_{AFP,i}$$

Then these values are used to estimate the surveillance sensitivity of the entire system; $CSe = 1 - ((1 - CSe_{AFP})(1 - CSe_{ENT})(1 - CSe_{ENV}))$.

As with other high-income countries sewage collects into a catchment area so maps from water companies can be used to determine the extent of population coverage if ENV is initiated at a specific sewage works. Composite samples are taken from the inlet of the sewage works and previous research suggests they have a high sensitivity to poliovirus if an individual is shedding within the last week.[3] Shedding studies have illustrated a high sensitivity of detecting poliovirus from just one composite sample and so the sensitivity of ENV is largely influenced by the frequency of sampling. If an individual sheds poliovirus for approximately 16 days,[3] poliovirus could be detected within sewage for up to 23 days from one individual, resulting in a monthly sampling frequency corresponding to a detection probability of (23+1)/30=0.80. The duration of shedding in IPV vaccinated individuals is lower,[1] but if more than one individual is shedding poliovirus the probability of detection would increase. To account for the known variation in shedding and uncertainty in the number of shedders the probability of detection is given wide confidence intervals and monte-carlo simulation is used to sample from these distributions (Table 3). Fortnightly sampling within one location would increase the detection probability to 1.00. Sensitivity of detection is thought to reduce with increasing sewage flow[4] and so sensitivity may be lower in sewage sites processing wastewater from a large (>100,000) population, but empirical studies that test this are lacking.

## 5. Estimation of the probability of being polio-free

Using the principal of the negative predictive value of a test, and assuming that testing has 100% specificity, the probability of being infection free within a given month ($t$) is $P(free_t) = (1-P)/(1-P.CSe_t)$, where $P$ is the prior for being infected and $CSe$ refers to diagnostic sensitivity, which in this case is the sensitivity of the surveillance system. Each prior probability is the $P(free_t)$ for the previous time period, which is a combination of being free during the previous time period and accounting for the probability of introduction. We also need to account for poliovirus introduction for each calendar month ($P(Intro_t)$). The probability of being infection free within a calendar month is then given as;

$$P(free_{t-1}) = 1 - (P(infect_{t-1}) + P(intro_{t-1}) - P(infect_{t-1}).P(intro_{t-1})) \quad \text{equation 4.1}$$

$$P(free_t) = (1 - P(free_{t-1}))/(1 - P(free_{t-1}).CSe_t \quad \text{equation 4.2}$$

Different sampling strategies are considered for ENV surveillance. The rate of poliovirus introduction is unknown, consequently the rate is estimated from approximating population movements to and from countries reporting poliomyelitis cases and the probability of shedding. From the International Passenger Survey (Figure 3) we can approximate the numbers of individuals that travel to and from countries reporting polio cases and combine this with the reported incidence of wild and VDPV within each country to provide an upper estimate of the rate of introduction. Low ($1x10^{-4}$), medium ($1x10^{-3}$) and high ($5x10^{-3}$) probabilities of poliovirus introduction per month were used to account the true value being unknown.

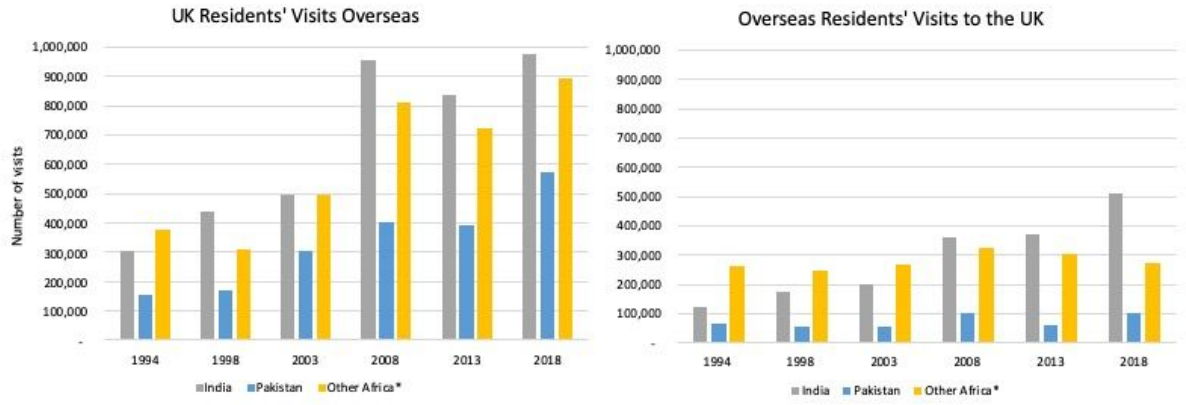



*Figure 3. Estimates of the number of visits to and from countries that have reported poliomyelitis cases (IPS data).*

## 6. Justification for probabilities used in the scenario tree modelling

In most probabilities estimated below, a mean and 95% confidence intervals are provided from the available data. These values were inputted to the model by specifying a beta distribution with parameters α and β. Within the software R, the specific parameter values that correspond to the specified mean and 95% confidence intervals were provided using the library 'prevalence'.

### Acute Flaccid Paralysis (AFP) Surveillance

- $Pr(case_{AFP})$: Of individuals infected with poliovirus Nathanson et al.[5] report that the probability of a clinical case varies by serotype; 0.005, 0.0005 and 0.0009 for serotypes 1, 2, and 3 respectively. A beta distribution with mean 0.005 and 95% CI 0.0005-0.009 encapsulates these estimated probabilities and the possible uncertainty in the values. As we estimate the sensitivity for wild poliovirus and vaccine-derived poliovirus separately, we use the estimates for serotype 1 and 2.
- $Pr(notification_{AFP})$: A case of AFP caused by poliovirus is an acute condition where it is very likely in a high income setting that healthcare will be sought. However, there is little data to inform this probability so we have taken precautionary principle of using knowledge from all cases of AFP (including Guillian-Barre syndrome) within England and Wales.
- $Pr(sample_{AFP})$: Stool sampling is recommended as part of the clinical investigation of all AFP cases. Within Salisbury et al. [6] of 0.54 of AFP cases had stool samples. Since this time clinical sampling has mostly likely improved, so we select a mean of 0.8 with confidence intervals ranging from 0.5-0.95.
- $Pr(test_{AFP})$: Samples to be tested for poliovirus undergo rigorous laboratory testing where PCR is used to determine the presence of enterovirus in stool, CSF or throat swabs. Following a positive PCR virus culture, intratypic differentiation and sequence analysis will be carried out as per the WHO protocol. The testing is highly sensitive with reported sensitivities above 0.95 for ~100 RNA copies per microlitre for ITD 5.0 which is a similar protocol to that used in testing within England and Wales[7]. We specify a high probability of detection with a mean of 0.97 and 95% CI of 0.95-1.00.

### Enterovirus (ENT) Surveillance

- $Pr(case_{ENT})$: Conditions such as aseptic meningitis are also clinical indicators of poliovirus infection in addition to acute flaccid myelitis. There are fewer reports of the probability of developing aseptic meningitis, but ~~Salisbury et al. [6] suggest that about 3% of case may lead to aseptic meningitis, and~~ Mehndiratta et al estimate that meningitis occurs in about 1% of cases,[8] although no distinction is made between serotype. Additionally, during a serotype 3 polio outbreak in Finland, nine cases of paralytic poliomyelitis were reported and one case of aseptic meningitis, which could

be used to suppose a 9:1 ratio of paralytic polio to aseptic meningitis.[9] Confidence intervals 0.01-0.05 were used to account for uncertainty in this estimate.

- Pr(notification$_{ENT}$): Clinical disease associated with enterovirus infection is used as a proxy for the notification rate that might be associated with aseptic meningitis caused by poliovirus infection. Estimates are not available but it is assumed that health-seeking behaviours would be similar to that for poliovirus infection
- Pr(sample$_{ENT}$): For clinical disease associated with enterovirus infection, Majumdar et al. [9] provide a description of current surveillance activities and report that a large proportion of clinical cases have microbiological samples (stool and CSF) that would enable culture of poliovirus. We assume an average probability of collecting a sample of 0.8 with wide confidence intervals (95% CI 0.5-0.95 to account for the large uncertainty in the estimate.
- Pr(test$_{ENT}$): The microbiological protocol for clinical samples via ENT surveillance is the same as AFP diagnostics, so the same probabilities are used.

Environmental (ENV) Surveillance

- Pr(shedding$_{ENV}$): We assume that all individuals infected with poliovirus shed poliovirus in stool.
- Pr(catchment$_{ENV}$): As sewerage systems in England and Wales consist of a convergent sewer system, we can assume that all waste will eventually reach a sewage processing plant. Each local authority is assumed to have at most one sewage treatment plant that can be sampled for ENV surveillance. In many areas, for example London, one sewage treatment plant serves several local authorities. Within the framework, if a local authority is assumed to be sampled during ENV surveillance, we assume a probability of 0.8 that the infected individuals would be sampled (to account for time spent outside of the sewage catchment area).
- Pr(sample$_{ENV}$): Sampling of wastewater is carried out using a composite sampler, which takes small samples of the wastewater over a 24 hour period [9]. If an individual sheds poliovirus for approximately 16 days,[3] poliovirus could be detected within sewage for up to 23 days from one individual, resulting in a monthly sampling frequency corresponding to a detection probability of (23+1)/30=0.80.
- Pr(test$_{ENV}$); The microbiological protocol for clinical samples via ENV surveillance is similar as AFP diagnostics, with an added concentration step (2-phase separation) [9]. It is not thought that the concentration step reduced detection sensitivity, but the large amount of contamination from mixed sewage may reduce culture success of poliovirus.

References

1. Hird, T. R. & Grassly, N. C. Systematic review of mucosal immunity induced by oral and inactivated poliovirus vaccines against virus shedding following oral poliovirus challenge. *PLoS Pathog.* **8**, (2012).

2. Cameron, A., Njeumi, F., Chibeu, D & Martin, T. RISK-BASED DISEASE SURVEILLANCE.

3. Lodder, W. J. *et al.* Feasibility of quantitative environmental surveillance in poliovirus eradication strategies. *Appl. Environ. Microbiol.* **78**, 3800–3805 (2012).

4. Hovi, T., Stenvik, M., Partanen, H. & Kangas, A. Poliovirus surveillance by examining sewage specimens. Quantitative recovery of virus after introduction into sewerage at remote upstream location. *Epidemiol. Infect.* **127**, 101–106 (2001).

5. Nathanson, N. & Kew, O. M. From emergence to eradication: the epidemiology of poliomyelitis deconstructed. *Am. J. Epidemiol.* **172**, 1213–1229 (2010).

6. Salisbury, D. M., Ramsay, M. E., White, J. M. & Brown, D. W. Polio eradication: surveillance implications for the United Kingdom. *J. Infect. Dis.* **175 Suppl 1**, S156-159 (1997).

7. Gerloff, N. *et al.* Diagnostic Assay Development for Poliovirus Eradication. *J. Clin. Microbiol.* **56**, (2018).

8. Mehndiratta, M. M., Mehndiratta, P. & Pande, R. Poliomyelitis. *The Neurohospitalist* **4**, 223–229 (2014).

9. Simonen, ML, Roivainen, M, Iber, J, Burns, C & Hovi, T. Outbreak of poliomyelitis in Finland in 1984-85-Re-analysis of viral sequences using the current standard approach. *Virus research.* 2010. 147(1); 91-97. doi: 10.1016/j.virusres.2009.10.012

109. Majumdar, M. *et al.* Isolation of Vaccine-Like Poliovirus Strains in Sewage Samples From the United Kingdom. *J. Infect. Dis.* **217**, 1222–1230 (2018).