PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A systematic review of the worldwide prevalence of survivors of poliomyelitis reported in 31 studies.
AUTHORS	Jones, Kelly; Balalla, Shivanthi; Theadom, Alice; Jackman, Gordon; Feigin, Valery

VERSION 1 - REVIEW

REVIEWER	Arend Voorman, PhD The Bill and Melinda Gates Foundation
REVIEW RETURNED	14-Dec-2016

GENERAL COMMENTS	The paper addresses what I think is an important issue: the residual disability left by a disease which is on the cusp of eradication. Indeed, this is the reason behind the Global Polio Eradication, and survivors of the disease have been some of the most valuable voices in the battle against it. Quantifying the size of this population would be a useful reminder of the value of prevention, especially in these final stages of eradication when incidence of disease is low enough to ignore for most of the world's population. The authors note the variety of prevalence estimates around the world, illustrating the relative differences in vaccination campaign effectiveness and also epidemiology of the disease in the years preceding the surveys reviewed. However, I feel there are a number of basic technical issues in the review which need to be corrected. First, the authors should provide more detail on the clinical manifestations (and lack thereof) of infection by poliovirus. 72% of infections result in no illness whatsoever, and fewer than 1% of those infected develop acute flaccid paralysis. Many of those, if not most, recover fully through compensation. A good place to start is Chapter 28 of Vaccines (Plotkin, 6th edition), and references contained there. Somehow this basic description is missing in the review, and necessary for any useful interpretation of current prevalence estimates, and indeed, even the definition of prevalence since most infections cause no lasting illness. Since rates of permanent paralysis are <1%, prevalence in the pre-vaccine era must also be <1%, and <<1% now, since incidence is extremely rare in the past few decades. Second, there are many other causes of acute flaccid paralysis, and

	it is thought that other causes of AFP occur at reasonably high rates, on the order of 1-3 per year per 100,000 under 15 years of age (see http://dx.doi.org/10.15585/mmwr.mm6513a3). Since polio can only be diagnosed based on stool culture or CNS examination after death, it seems strange that alternate causes of disease aren't mentioned. In contrast to what is stated in the paper, this fact might lead lameness surveys to overstate the prevalence of polio, particularly in areas like India where non-polio AFP incidence is exceptionally high. Lastly, and perhaps most importantly, polio has been extremely rare in the past few decades due to widespread polio vaccination. The vast majority of papers are quite old, most were published more than 30 years ago, and thus not very relevant to current prevalence without some nuanced demographic extrapolation that take into account the lack of incidence in the ensuing years, and likely low survival rates of paralyzed children in many of these settings. Is the purpose of the paper to estimate historical prevalence, or current prevalence? Minor comments Page 5: • Throughout, particularly in the abstract, it would be useful to cleanly distinguish between poliomyelitis (disease causing acute flaccid paralysis) and poliovirus (the viral agent). The paper refers to what most would refer to as 'prevalence of residual paralysis due to poliomyelitis', rather than 'polio' which is often used to indicate incidence or infection with poliovirus. E.g. polio eradication refers to stopping transmission of poliovirus, and no new incidence of poliomyelitis. • Line 11: Polio was likely endemic for 1000s of years, and remains endemic in Pakistan, Nigeria, and Afghanistan. Its epidemiology was increasingly characterized by outbreaks from the late 1800s onwards. • Line 16: Poliovirus is an enterovirus, and only infects the mucosa in the vast majority of cases. In rare instances (<1%) poliovirus infections cause any sort of muscle weakness. • Line 25: The number of polio AFP cases in the 1980s has been estimated at around 400,000 per year. Widespread AFP surveillance was not conducted at the time, and so many fewer (50,000 referred to) were reported. • Line 27: The figure is much lower currently. At the time of writing, there are 37 cases of polio AFP (http://polioeradication.org/polio-today/polio-now/). • Line 50: I'm unaware of any quarantine requirements for polio implemented or recommended in the recent past. AFP surveillance is quite robust for the last 15-20 years in much of the world. It would be useful to have a citation for this figure. • Line 52: This statistic (11%) is not accurate. It is possible that this was true when the referenced article was written

	(1993), and that birth cohorts are the relevant population for prevalence surveys. Page 10 • Line 44 & 55: I would think that prevalance of poliomyelitis refers specifically to those living with residual disease, and this would not be a limitation of the studies. Since the vast majority of poliovirus infections result in temporary flu-like symptoms, those without any residual disease aren't relevant. • Line 55: Note that children 0-6 months old are protected by maternal antibodies, and have extremely low incidence of poliomyelitis. Looking through the studies in Table 1, I don't see any in that age range. One (Soudarssane 1993) is in 0-6 years old

REVIEWER	NEAL NATHANSON U PENNSYLVANIA USA
REVIEW RETURNED	20-Dec-2016

GENERAL COMMENTS	I NEED TO PROVIDE A BIT OF CONTEXT THIS IS A META ANALYSIS OR REVIEW OF PUBLISHED STUDIES THESE STUDIES ARE FOCUSED ON THE FOLLOWING ISSUE. SUBJECTS WHO EXPERIENCE PARALYTIC POLIOMYELITIS MAY BE LEFT WITH VARIABLE DEGREES OF PARALYSIS, FROM NONE TO SEVERE, EXCLUDING THOSE WHO DIE DURING THE ACUTE PHASE OF INFECTION. OVER MANY YEARS A NUMBER OF PARALYSED VICTIMS ACCUMULATE IN THE POPULATION. THIS STUDY ASKS: WHAT IS THE PREVALENCE OF THESE ACCUMULATED NUMBERS OF VICTIMS. THERE ARE SEVERAL PROBLEMS HERE. FIRST, IS THIS A QUESTION OF IMPORTANCE COMPARED TO THE REAL LIFE ISSUES AROUND THE GLOBAL POLIO ERADICATION EFFORT? NO ONE IN THE FIELD THAT I AM AWARE OF IS INTERESTED IN THE QUESTION OF PREVALENCE, WHICH IS PAST HISTORY. SECOND, ARE THE DATA ANY GOOD. OR IS THIS GINGO, GARBAGE IN GARBAGE OUT? THE DATA CITED SHOW A VERY WIDE VARIATION IN PREVALENCE. LIKELY THIS REFLECTS THE VAST SPREAD IN THE QUALITY OF THE DATA COLLECTED. IT WOULD TAKE A MAJOR INVESTMENT TO SORT THROUGH ALL THE LAMENESS AND OTHER INSTANCES OF DISABILITY AND IDENTIFY WITH CERTAINTY THOSE WHICH WERE RESIDUAL PARALYTIC POLIO. LIKELY THIS HAS NOT BEEN DONE IN MOST OF THESE STUDIES. SO WHY WOULD ONE WANT TO PUBLISH A REVIEW OF VERY

	QUESTIONABLE DATA THAT DOES NOT INFORM OR ADDRESS A CURRENT HEALTH ISSUE? I SUSPECT THIS WAS A STUDENT EXERCISE THAT SOMEONE WOULD LIKE TO PUBLISH. BUT I DON'T THINK IT BELONGS IN THE BMJ

VERSION 1 – AUTHOR RESPONSE

Comments from and responses to Reviewer # 1

Comment: The authors should provide more detail on the clinical manifestations (and lack thereof) of infection by poliovirus. 72% of infections result in no illness whatsoever, and fewer than 1% of those infected develop acute flaccid paralysis. Many of those, if not most, recover fully through compensation. A good place to start is Chapter 28 of Vaccines (Plotkin, 6th edition), and references contained there. Somehow this basic description is missing in the review, and necessary for any useful interpretation of current prevalence estimates, and indeed, even the definition of prevalence since most infections cause no lasting illness. Since rates of permanent paralysis are <1%, prevalence in the pre-vaccine era must also be <1%, and <<1% now, since incidence is extremely rare in the past few decades.

Response: While we were unfortunately unable to access Chapter 28 of Vaccines (Plotkin, 6th edition), the following details of the clinical manifestations of infection by poliovirus are now included in the Introduction section – Polio, a human enterovirus [2], primarily affects children aged <5 years with infection most commonly spread by the faecal-oral route. Up to 75% of poliovirus infections in children are asymptomatic, while approximately 24% of cases may experience a low grade fever and sore throat [6]. Less than 1% of cases experience viral replication in the central nervous system causing temporary or permanent paralysis (known as poliomyelitis).[3]

Comment: There are many other causes of acute flaccid paralysis, and it is thought that other causes of AFP occur at reasonably high rates, on the order of 1-3 per year per 100,000 under 15 years of age (see http://dx.doi.org/10.15585/mmwr.mm6513a3). Since polio can only be diagnosed based on stool culture or CNS examination after death, it seems strange that alternate causes of disease aren't mentioned. In contrast to what is stated in the paper, this fact might lead lameness surveys to overstate the prevalence of polio, particularly in areas like India where non-polio AFP incidence is exceptionally high.

Response: We thank the reviewer for their efforts in directing us to additional and valuable resources. Other causes of acute flaccid paralysis are now acknowledged in the Discussion section, as follows – Alongside methodological concerns discussed above, rather than informing estimates of the prevalence of survivors of poliomyelitis worldwide, limitations in the literature render this review largely of the historical prevalence of residual acute flaccid paralysis (AFP) that may be due to poliomyelitis. AFP is a clinical syndrome with a broad array of possible etiologies (i.e., spinal cord compression, trauma, exposure to chemicals, recent illness) that serves as a proxy for poliomyelitis [15]. Figures from AFP surveillance surveys, an essential strategy of the Global Polio Eradication Initiative [14], suggest that non-polio AFP affects 1-3 cases per 100,000 children aged <15 years per year [16]. Subsequently lameness surveys, most common in this review, risk overstating the prevalence of survivors of polio. Such risks are especially high in areas such as Afghanistan, India and Nigeria who have the highest annualized non-polio AFP rate compared with the number of poliovirus cases [17]. It is therefore possible that the international prevalence estimates from lameness surveys included in this review over-estimate the prevalence of survivors of poliovirus infection who developed poliomyelitis.

Comment: Polio has been extremely rare in the past few decades due to widespread polio vaccination. The vast majority of papers are quite old, most were published more than 30 years ago, and thus not very relevant to current prevalence without some nuanced demographic extrapolation that take into account the lack of incidence in the ensuing years, and likely low survival rates of paralyzed children in many of these settings. Is the purpose of the paper to estimate historical prevalence, or current prevalence?

Response: The limitations of previous research have been further acknowledged throughout the paper, including the following updates –
Abstract: Results section – Historical lameness surveys of children predominated, with wide variation in case definition and assessment criteria, and limited relevance to current prevalence given the lack of incidence of poliovirus infection in the ensuing years.
Discussion: As mentioned above, this section now reads - Alongside methodological concerns discussed above, rather than informing estimates of the prevalence of survivors of poliomyelitis worldwide, limitations in the literature render this review largely of the historical prevalence of residual AFP that may be due to poliomyelitis. AFP is a clinical syndrome with a broad array of possible etiologies (i.e., spinal cord compression, trauma, exposure to chemicals, recent illness) that serves as a proxy for poliomyelitis [15]. Figures from AFP surveillance surveys, an essential strategy of the Global Polio Eradication Initiative [14], suggest that non-polio AFP affects 1-3 cases per 100,000 children aged <15 years per year [16]. Subsequently lameness surveys, most common in this review, risk overstating the prevalence of survivors of polio. Such risks are especially high in areas such as Afghanistan, India and Nigeria who have the highest annualized non-polio AFP rate compared with the number of poliovirus cases [17]. … Our findings suggest the average crude worldwide prevalence of 295/100,000 person years. However, given many of the studies included in this review were undertaken in geographical areas where rates of non-polio AFP are high, the dated nature of studies (many being published more than 30 years ago) and since aging population, and the 99% reduction in the incidence of poliovirus infection, it must be noted that the actual worldwide prevalence is likely much lower.

We have also revisited the manuscript to show a clear focus on estimating the current prevalence of survivors of poliomyelitis following poliovirus infection.

Questions from and responses to Reviewer # 2

Question: 1) Q. IS THIS (the prevalence of polio) A QUESTION OF IMPORTANCE COMPARED TO THE REAL LIFE ISSUES AROUND THE GLOBAL POLIO ERADICATION EFFORT?

Response: Reviewer 1 states “The paper addresses what I think is an important issue: the residual disability left by a disease which is on the cusp of eradication. Indeed, this is the reason behind the Global Polio Eradication, and survivors of the disease have been some of the most valuable voices in the battle against it. Quantifying the size of this population would be a useful reminder of the value of prevention, especially in these final stages of eradication when incidence of disease is low enough to ignore for most of the world’s population.”

Evidence of the importance and interest in sound scientific research examining aspects of the polio beyond eradication figures is also evident in scientific literature. A search of MEDLINE via PubMed using a single search term ‘post-polio’, for example reveals 106 manuscripts published in the last 5 years alone. The focus of such publications is wide and varied, including QoI outcomes, post-polio management, genetic contributions, epidemiological profiles, incidence, interventions, and physical disability. The attendance of 290 delegates at the recent 3-day ‘Australasian-Pacific Post-Polio Conference’ held in Sydney, Australia, September 2016 further attests to the interest in polio beyond ‘…the real life issues around the global eradication effort’. Further, PostPolio Health International

(PHI) is a non-profit organisation whose mission is to enhance the lives, health, and independence of polio survivors. Adopting the slogan 'WE'RE STILL HERE!', in 2016 PHI awarded $100,000 for new research examining the effects of polio. Prevalence estimates as presented in our manuscript are required to inform better understanding of the potential scale of such effects.

The recognized importance of focusing not only on polio eradication but also the scale of the aftermath of the virus is evident in the following - Hill (2015) states "…PPS affects an estimated 120,000 people in the UK, a figure believed to be similar to the number of people with Parkinson's and other serious neurological conditions. So surely it is not too much to ask that PPS receives the same attention from the caring professions and the public?" (p.30).
Hill (2015). People living with post-polio syndrome must not be forgotten. Nurs Stand, 30(10):30-31. http://dx.doi.org/10.7748/ns.30.10.30.s38.

Comment: 2) NO ONE IN THE FIELD THAT I AM AWARE OF IS INTERESTED IN THE QUESTION OF PREVALENCE, WHICH IS PAST HISTORY.

Response: The section above disproves this comment. Further, our review presents an important historical summary of international poliomyelitis prevalence data. No previous worldwide summary has been provided.

Question: 3) Q. ARE THE DATA ANY GOOD? THE DATA CITED SHOW A VERY WIDE VARIATION IN PREVALENCE. LIKELY THIS REFLECTS THE VAST SPREAD IN THE QUALITY OF THE DATA COLLECTED.

Response: The variable quality of study data is acknowledged in the manuscript. Reviewer 1 also adds that the variety of prevalence estimates around the world likely illustrates the relative differences in vaccination campaign effectiveness and epidemiology of the disease in the years preceding the surveys reviewed. Regardless of whether the findings of systematic reviews reveal consistent or largely variable data, the purpose is to present a summary of the current status of the literature. This is achieved by the above manuscript with the conclusion that more accurate prevalence data are needed to accurately determine the numbers of people living with the effects of polio.

Question: 4) Q. WOULD ONE WANT TO PUBLISH A REVIEW OF VERY QUESTIONABLE DATA THAT DOES NOT INFORM OR ADDRESS A CURRENT HEALTH ISSUE?

Response: There are an estimated 12-20 million individuals living with polio sequelae worldwide (Gonzalez, 2010), rendering polio a significant health issue for those directly affected and their informal caregivers. Our systematic review informs understanding by clearly highlighting the need for more accurate estimates to better inform the prioritization of services and supports for those directly affected and their caregivers. Before this can be achieved, it is necessary to synthesize current research examining prevalence estimates. Gonzalez, H., Olsson, T, and Borg, K. (2010). Management of postpolio syndrome. The Lancet Neurology, 9(6): 634 e642.

Comment: 5) I SUSPECT THIS WAS A STUDENT EXERCISE THAT SOMEONE WOULD LIKE TO PUBLISH.

Response: A team of senior researchers at the National Institute for Stroke and Applied Neurosciences conducted this systematic literature review. This research was not undertaken as a student project. The research was initiated and undertaken collaboratively with Polio New Zealand Inc. The initial impetus for the study came from the Ministry of Health New Zealand to inform policy and government lobbying efforts. All aspects of the review were informed by a team of researchers with extensive experience in the undertaking of high quality epidemiological studies, with key skills in

determining prevalence rates. The study team included a certified neurologist and epidemiologist. Funded by provided by New Zealand's largest polio philanthropic provider, The Sir Thomas and Lady Duncan Trust, this review forms the basis for further planned research to determine more accurately the prevalence, outcomes and needs of those living post-polio and their caregivers. Providing clear evidence of the need for high quality epidemiological studies of polio survivors is the first fundamental step towards enhancing outcomes.

We sincerely appreciate the opportunity to further refine this manuscript ready for publication in BMJ Open and patiently await a final decision. We thank both reviewers for their contributions to this process.