

Title: The public health control of scabies: priorities for research and action

Short title: Research priorities for scabies control

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2 **Summary**

3 Scabies is a parasitic disease of the skin that disproportionately affects disadvantaged
4 populations. Scabies causes considerable morbidity and leads to severe bacterial infection and
5 immune-mediated disease. Recent scientific advances suggest that scabies is amenable to
6 population-level control, particularly through mass drug administration. In recognition of
7 these issues, WHO added scabies to the list of neglected tropical diseases (NTDs) in 2017. In
8 order to develop a global control program, key operational research questions must now be
9 addressed. Standardised approaches to diagnosis and methods for mapping are required to
10 further understand the burden of disease. The safety of treatments for young children,
11 including with ivermectin and moxidectin, should be investigated. Studies are needed to
12 inform optimum implementation of mass treatment, including the threshold for intervention,
13 target, dosing, and frequency. Frameworks for surveillance, monitoring and evaluation of
14 control strategies are also necessary.

15

16 **Introduction**

17 In 2017, scabies was added to the World Health Organization (WHO) list of neglected
18 tropical diseases (NTDs). Scabies was recommended to be included as a ‘category A’ NTD,
19 defined as those conditions that fulfil all four specified criteria, and are recommended for
20 large scale action in the portfolio of the NTD Department.¹ In reaching this recommendation,
21 the WHO NTD Strategic and Technical Advisory Group noted the need for further research
22 to inform control strategy as well as key issues for programmatic implementation, including
23 ensuring affordable access to oral medications and developing guidelines for their public
24 health use.² In March 2018, the WHO NTD Global Working Group on Monitoring and
25 Evaluation discussed scabies for the first time. Key recommendations from that meeting
26 included the need to better define the global burden; to integrate control efforts to capitalise
27 on ivermectin-based programs for other NTDs; and to establish interim guidelines for public
28 health interventions for scabies control.³ In this rapidly evolving context, we review major
29 recent advances in the science of control of human scabies, and identify key operational
30 research questions that need to be addressed to develop a global scabies control program.

31 **The burden of scabies**

32 Scabies is caused by infestation with the microscopic ectoparasite *Sarcoptes scabiei* var.
33 *hominis*, and leads to severe itch, skin lesions and more serious complications due to bacterial
34 superinfection (Figure 1). Transmission requires skin-to-skin contact, and there is no non-
35 human reservoir. Scabies occurs in all countries, but its distribution is not uniform. In high-
36 income settings, most cases are sporadic, and the predominant public health issue is the
37 management of outbreaks in institutions such as hospitals and residential aged care facilities.
38 A far greater burden of disease is found in low- and middle-income countries, where access
39 to effective treatment is limited and population crowding increases the opportunities for
40 transmission. Areas with hot, humid climates have the highest reported prevalence, most
41 prominently island communities in the Pacific region and Central America, and Indigenous
42 communities of northern Australia.⁴⁻⁶ In these settings, the community prevalence has been
43 consistently estimated in the range of 20 – 30%, with a higher prevalence of up to 40 – 50%
44 in children aged less than 18 years (Figure 2).⁷⁻⁹

45 In other resource-limited settings where baseline prevalence is lower, change in
46 environmental or socio-political conditions can be associated with epidemics,¹⁸ such as the

47 outbreak in the Amhara Region in Ethiopia that has been in progress since 2015 and has been
48 estimated to affect more than one million people.^{19,20} Circumstances with substantial
49 population crowding frequently lead to high levels of transmission, and outbreaks are
50 common within schools, prisons and camps for refugees and internally displaced persons.²¹

51 Scabies is one of the world's most common illnesses. The Global Burden of Disease (GBD)
52 Study 2016 estimated the global point prevalence of scabies to be around 147 million, with
53 455 million annual incident cases.²² Further GBD analyses estimated that scabies caused
54 approximately 3.8 million disability-adjusted life years (DALYs), ranking scabies as one of
55 the most important NTDs.²³ Scabies causes an age-adjusted morbidity burden similar to
56 *Haemophilus influenzae* type B meningitis and acute lymphoid leukaemia.²⁴ These GBD
57 analyses are modelled on the small number of published reports on the prevalence of scabies.
58 Of note, the disability weighting only considers the skin changes and itch directly caused by
59 infestation.²⁴ The estimated burden would be far greater if the morbidity and mortality caused
60 by the complications of scabies were included (Figure 3). Scabies infestation causes a
61 considerable proportion of bacterial skin infection (pyoderma) in many resource-limited
62 settings, most commonly manifesting as infected sores (impetigo).^{7,8,25,26} For example,
63 Aboriginal children in Australia were 12 times more likely to develop impetigo when
64 infected with the scabies mite,²⁶ and studies from Pacific island nations have estimated the
65 attributable risk of scabies as a cause of impetigo to be 41% – 93%.^{7,8,27} Scabetic lesions and
66 traumatic scratching create breaches in the skin barrier that are a portal for bacterial entry.
67 Scabies mite components such as serpins inhibit innate immune pathways including
68 neutrophil function and directly promote the growth of *Staphylococcus aureus* and
69 *Streptococcus pyogenes*.²⁸⁻³¹ Skin infection due to these bacteria can lead to severe soft
70 tissue infections and invasive disease. Infection with *S. pyogenes* can also lead to immune-
71 mediated complications including post-streptococcal glomerulonephritis and possibly acute
72 rheumatic fever, which in turn contribute to chronic kidney disease and rheumatic heart
73 disease (Figure 3).^{32,33} Quantification of the proportion of the burden of these serious health
74 consequences attributable to scabies will give a more accurate estimate of the global burden
75 of scabies and the potential benefit of scabies control.

76 **Diagnosis**

77 Both the mapping of scabies and population-level control are hampered by the lack of a
78 reliable, reproducible and standardised approach to diagnosis. Two systematic reviews of

79 diagnostic methods found a lack of consistency in the approach to scabies diagnosis.^{34,35}
80 Microscopy of skin scrapings to visualise mites and eggs is highly specific but insensitive and
81 operator dependent, and therefore generally not useful for field settings. In order to address
82 this gap, an international panel of experts, convened by the International Alliance for the
83 Control of Scabies (IACS) recently used a Delphi consensus method to develop the 2018
84 IACS Criteria for Scabies Diagnosis in research and epidemiological settings.³⁶ These criteria
85 enable diagnosis and reporting in three bands of diagnostic certainty - confirmed, clinical and
86 suspected scabies. A diagnosis of confirmed scabies requires identification of the mite on
87 microscopy or non-invasive visualisation techniques such as videomicroscopy and
88 dermoscopy.³⁷ Clinical and suspected scabies categories rely on features of clinical history
89 and examination. As such, the criteria can be adapted for use in a variety of settings,
90 including field surveys, and may help to standardise reporting and the conduct of scabies
91 research. Validation of these criteria in diverse environments is now required, followed by
92 development of standardised training methods and materials.

93 Although the current focus should be on development of diagnostics for mapping and
94 surveillance, in future, objective diagnostic tests may be needed, particularly if areas of low-
95 endemicity transition to a target of disease elimination. A point-of care diagnostic test would
96 be ideal for public health use. Direct skin-based testing for infestation using molecular
97 techniques, including polymerase chain reaction^{38,39} and loop mediated isothermal
98 amplification,⁴⁰ have been proposed but none are currently ready for programmatic use.
99 Development of ELISA-based tests to detect antibodies against scabies antigens⁴¹ has been
100 hindered by cross-reactivity between antigens from scabies and house dust mites.^{42,43} If a
101 specific antibody test for scabies was developed, in order for it to be diagnostic, further
102 evaluation would need to ensure that measured antibody responses were directly associated
103 with ongoing infestation and not a measure of previous exposure.

104 In addition to molecular diagnostics, non-invasive mite visualisation methods should be
105 further evaluated. These high-magnification methods allow direct, in vivo visualisation of the
106 mite (and with some methods, determination of mite survival or demise after treatment)
107 without extraction of the mite by skin-scraping.^{44,45} Although these devices are expensive and
108 require specialised training, more simple and affordable videomicroscopes also permit
109 accurate visualisation of the mite in vivo, and low cost dermatoscopes have been
110 developed.^{46,47} Further investigation and standardisation of outcome measures using these

111 methods would assist in assessing the efficacy of new treatments, and possibly validation of
112 mapping and confirmation of outbreaks.⁴⁸

113 **Epidemiology and mapping**

114 Despite an expansion of research on scabies in the last decade, the development of a global
115 strategy has been constrained by a lack of prevalence data from most countries, including
116 those suspected to be at-risk based on routinely reported clinical data or geographic or
117 socioeconomic characteristics. For example, a worldwide systematic review of published
118 scabies prevalence estimates found 48 studies, of variable quality, with over-representation of
119 countries in the Pacific region and large areas of the world having no published prevalence
120 data.⁴ Experience from other NTDs suggests that the knowledge of disease burden gained
121 through mapping is critical for stakeholder engagement, translational research and successful
122 scale-up of control programs.⁴⁹

123 Given the logistic challenge and cost of detailed mapping for NTDs,⁵⁰ a priority activity is the
124 development of a simple, low-cost, rapid assessment tool to assist policy-makers in initially
125 determining whether scabies is likely to be a public health problem in a given context.
126 Standardised survey methods to map scabies prevalence would then be required for a more
127 detailed estimate of disease burden and its variation within and between regions. Survey
128 methods could utilise the 2018 IACS Diagnostic criteria,³⁶ if these criteria are found to be
129 valid and reproducible. It may be possible to train non-expert examiners in a limited, brief
130 skin examination, which could then be correlated with more detailed diagnostic methods.⁵¹ A
131 similar approach has been used for trachoma, where a rapid assessment may be followed by a
132 standardised mapping survey.⁵²⁻⁵⁵ Survey design will need to consider the most appropriate
133 populations and settings in which to conduct mapping, including ease of access, spatial and
134 age distributions of disease and community acceptability. For example, mapping of children
135 attending school could be expected to provide a representation of the groups with the highest
136 burden in a community. This may be efficient, practicable and amenable to integration with
137 mapping for some other NTDs and other health and education programs.^{56,57} Formal
138 comparison of school versus community based sampling would help determine how well
139 school prevalence correlates with community prevalence.^{58,59}

140 Beyond national-level prevalence data, there is limited understanding of the epidemiology of
141 specific high burden areas or populations within otherwise high-income or low-prevalence

142 settings. Recognized examples include disadvantaged Indigenous populations within
143 Australia, New Zealand and Canada,^{26,60-62} imprisoned ^{63,64} and homeless populations,⁶⁵ and
144 among groups seeking asylum within Europe.⁶⁶⁻⁶⁸ Scabies is a disease of poverty and inequity
145 and it is likely that sub-populations with higher burdens would be found in many otherwise
146 high-income settings.⁶⁹

147 Institutional scabies outbreaks result in considerable morbidity, stigma and healthcare cost in
148 high-income settings. These outbreaks are typically challenging to identify and manage,
149 leading to lengthy delays in confirmation and control as well as substantial cost.⁷⁰⁻⁷³ Changes
150 in social demography, particularly aging, mean that these outbreaks may become more
151 common, and the development of appropriate public health strategies is therefore warranted.
152 A deeper appreciation of the features of institutional outbreaks in high-income settings could
153 be leveraged for control of scabies elsewhere.

154 **Transmission and complications**

155 Despite scabies being an ancient disease, our understanding of the drivers of transmission
156 remains limited. Understanding transmission dynamics is important for investigating the
157 comparative effects of different control strategies, including through mathematical
158 modelling.^{74,75} The observed cycles of scabies prevalence in some temperate settings (leading
159 to the misnomer “the seven-year itch”) previously raised the possibility of herd immunity.
160 However, in many tropical settings, recurrent infestations are common and present with more
161 rapid onset of symptoms than in the initial infection.⁴³ Very high population prevalence is
162 sustained in some of these settings, suggesting that variations across geographic regions and
163 time are more likely explained by factors other than personal or herd immunity.^{76,77}

164 Of particular importance to transmission is the role of individuals with the rare clinical
165 variant of crusted scabies (previously known as Norwegian scabies), usually in association
166 with immunosuppression (disease or drug-related) or neurological illness. People with
167 crusted scabies may carry thousands to millions of mites and are highly infectious, thereby
168 acting as core transmitters within some communities.⁷⁸ Failure to identify and manage these
169 individuals may undermine the success of control programs.⁷⁹ There is an incomplete
170 understanding of why there are many individuals in northern Australia with crusted scabies in
171 the absence of identifiable causes of immunosuppression, but relatively few such cases have
172 been described in other high-prevalence settings.^{7,78,80,81}

173 The pathogenic links between scabies, impetigo, the infectious complications of *S. aureus*
174 and *S. pyogenes* and the immune-mediated complications of *S. pyogenes* need further
175 investigation. If these high morbidity and mortality conditions can be more definitively
176 linked with scabies, and can be shown to be effectively prevented through scabies control, the
177 rationale to invest in scabies control will be more compelling for governments, potential
178 donors and other stakeholders. The relevant associations have been considered most
179 thoroughly in the Pacific region,^{61,82-84} where impetigo is very common, but the limited data
180 from other regions suggest endemic scabies occurs in those environments with lower
181 prevalence of impetigo.⁴ This pattern needs to be properly quantified and the reasons for any
182 variation, if genuinely present, further explored. Impetigo caused by *S. pyogenes* is a major
183 cause of acute glomerulonephritis,⁸⁵ which in turn contributes to the high burden of chronic
184 kidney disease in low-income settings.⁸⁶ Scabies has been associated with chronic kidney
185 disease in both epidemiological studies and case reports.⁸⁷⁻⁸⁹ Rheumatic heart disease is
186 estimated to cause over 300,000 deaths per year, with a global distribution that overlaps with
187 areas highly-endemic for scabies.⁹⁰ A global resolution on rheumatic fever and rheumatic
188 heart disease was adopted by the World Health Assembly in 2018.⁹¹ Primary prevention of
189 streptococcal skin infection through scabies control could potentially be an important
190 component of preventing these diseases.⁶¹

191 **Social and economic issues**

192 As a disease that affects the skin, scabies is a potent cause of stigma and reduced quality of
193 life.^{11,92,93} Increasingly, the chronic disfigurement caused by scabies and other NTDs is
194 understood to adversely affect mental health,^{56,94} although this aspect has not been factored
195 into current GBD estimates of DALYs. Understanding the conception of scabies, itch and
196 impetigo within various cultures will help define what ‘scabies as a public health problem’
197 means to the most affected communities. This research will also assist in building
198 partnerships with communities to develop control intervention, and to maximise participation
199 in them. Scabies is often incorrectly attributed to ‘poor hygiene,’ which may lead to stigma,
200 shame and reduced health-seeking. However, hygiene and handwashing do not affect the mite
201 or transmission,⁹⁵ and highly effective control has been demonstrated without any measures
202 addressing hygiene or environment (see below),⁹⁶ suggesting that associations with situations
203 of poverty and disadvantage are likely due to poor access to healthcare and treatment, or the
204 effects of overcrowding.^{21,97} The economic burden of scabies in some areas is thought to be

205 substantial, particularly due to the infestation leading to absence from employment and
206 education, as well as the direct costs of accessing healthcare and repeated treatments (Figure
207 3).⁹⁸ Economic studies of the costs of scabies infestation and complications are needed to
208 define and advocate for the most cost-effective control strategies.

209 **Treatment**

210 Although there are a number of effective, topical preparations for treatment of individual
211 cases, for multiple reasons these agents are poorly suited to population-level control
212 interventions. Reasons include the prolonged duration of application required and local
213 irritation, resulting in inadequate adherence.⁹⁹ Permethrin 5% cream is the most effective
214 topical treatment,¹⁰⁰ but is expensive and unavailable in most countries.²¹ Topical treatments
215 that are available in some low- and middle-income countries include benzyl benzoate and
216 sulphur ointments, but these are less well tolerated. Both options commonly cause skin
217 irritation and stinging after application, and sulphur ointments are messy, malodourous and
218 require repeat treatments.²¹ The effectiveness and safety profile of novel topical agents,
219 including tea tree oil, for individual case management should be further explored.¹⁰¹⁻¹⁰⁸

220 Oral medicines have clear advantages for treatment of asymptomatic individuals, and
221 particularly for treatment of whole populations through mass drug administration (MDA),
222 where oral medications are more likely to be accepted and ingestion can be directly observed.
223 Oral ivermectin is highly effective against scabies. Due to the lack of ovicidal action, a
224 second treatment is usually recommended after 7-14 days for individual treatment, to kill
225 newly hatched mites. A recent Cochrane review did not find any difference in efficacy when
226 one dose was compared with two doses of ivermectin, or between oral ivermectin and topical
227 permethrin.¹⁰⁹ Although the strength of the review conclusions was limited by the quality of
228 included studies, available evidence suggests that a single dose of ivermectin has some
229 efficacy, and that two doses are likely to be comparably effective to permethrin for individual
230 treatment. There is extensive experience on the feasibility and safety of using ivermectin for
231 MDA for other NTDs such as lymphatic filariasis and onchocerciasis.¹¹⁰

232 An oral agent with a longer duration of activity in the skin, that could persist for sufficient
233 time to kill newly hatched mites, would obviate the need for a second dose and represent a
234 major advance. Slow-release formulations of ivermectin have been developed, providing
235 potential therapeutic effect for up to 6 months.¹¹¹ These warrant further investigation for

236 scabies, although if the dosage form is large, administration to children may be challenging.
237 Moxidectin, a macrocyclic lactone anti-parasitic agent related to ivermectin, has a half-life of
238 up to 43 days, with prolonged activity in the skin.^{112,113} It is effective against *Sarcoptes*
239 infestations in animals, and in a pre-clinical trial using a porcine-model of scabies, single
240 dose moxidectin was superior to two doses of ivermectin based on the primary outcome
241 measure of mite score.¹¹⁴ Moxidectin has recently been approved by the United States Food
242 and Drug Administration (FDA) for treatment of onchocerciasis in individuals aged 12 years
243 and above.¹¹⁵ Clinical trials of moxidectin for scabies have now commenced, with a plan to
244 develop palatable products for children.¹¹⁶

245 Research into scabies treatments also needs to consider safety, including treatment of
246 pregnant and breastfeeding women and small children, groups that carry a disproportionate
247 burden of scabies and are responsible for much its transmission. Administration of topical
248 treatment to these groups during ivermectin-based MDA is a major cost and logistic issue.
249 Due to the inadequacy of existing safety data, use of ivermectin in MDA programs for other
250 NTDs has been restricted to those weighing over 15 kg or measuring above 90 cm (or aged 5
251 years or older in some settings). It is worth noting, however, that several studies have
252 reported no significant adverse outcomes from clinical and inadvertent public health use in
253 young children.^{117,118} Further investigation of the safety of ivermectin in young children, and
254 prospective data on the safety of moxidectin, are priorities. Ivermectin is considered a
255 pregnancy category C drug by the FDA, but this determination is based on animal studies that
256 used doses far in excess of those recommended for people.¹¹⁹ Studies comparing inadvertent
257 treatment in pregnant women to controls have not demonstrated any concerning safety
258 signal.¹²⁰⁻¹²³ In other NTD programs, ivermectin is offered when the risk of disease is
259 considered higher than the theoretical risk to the foetus.¹²⁴ In France, ivermectin is a
260 recommended second-line treatment for scabies during pregnancy.¹²⁵ Ivermectin is excreted
261 in very low concentrations in human milk, and is generally regarded as safe in lactating
262 women after the infant is 7 days old. Ivermectin can cause serious adverse events in
263 individuals with high blood counts of *Loa Loa* microfilariae, a parasite found in Central
264 Africa. Development of new diagnostic technologies such as the Loascope may enable safe
265 delivery of ivermectin MDA in these areas,¹²⁶ but further investigation of implementation is
266 needed.¹²⁷

267 In order to capitalise on existing MDA platforms for other NTDs, the safety of co-
268 administration of ivermectin with other medications needs to be established. In addition to the
269 long-standing practice of co-administration with albendazole, large-scale studies have now
270 demonstrated the safety of co-administration with azithromycin, opening the possibility of
271 integrating control of scabies with control of yaws and/or trachoma.¹²⁸⁻¹³⁰ Similarly, early
272 analysis of a multi-national safety cohort study of combination therapy of ivermectin,
273 diethylcarbamazine and albendazole (IDA) for lymphatic filariasis did not reveal safety
274 concerns and administration of this combination of agents has now been recommended for
275 specific epidemiological contexts within WHO guidelines.¹³¹⁻¹³⁴

276 Monitoring for development of resistance of mites to acaricides will also be important. There
277 have been isolated case reports of resistance to ivermectin in patients with crusted scabies
278 who received repeated and prolonged treatment.¹³⁵⁻¹³⁷ Annual MDA may be less likely to
279 promote the development of resistance than repeated individual treatments, but there is a lack
280 of evidence on this subject.¹³⁸ The proposed use of ivermectin MDA for malaria control^{119,139}
281 could also promote resistance, particularly if a strategy of multiple doses each month is
282 used.¹⁴⁰ However, the risk of resistance seems to be greater for intestinal helminths than
283 ectoparasites, based on experiences in livestock, where resistance to ivermectin among
284 intestinal parasites is now widespread.^{141,142} Increasing use of topical treatments for other
285 conditions in humans, such as permethrin for head lice and topical ivermectin for rosacea,
286 may also promote resistance in scabies mites.¹⁴³

287 Detailed treatment guidelines for scabies have been developed in several high-income
288 countries and regions, but recommendations vary.¹⁴⁴⁻¹⁴⁶ Standardised, evidence-based
289 treatment guidelines for resource-limited settings, including individual case management and
290 management of outbreaks in institutions or closed communities, would be valuable. Further
291 investigation and development of guidelines for the appropriate treatment for individuals with
292 crusted scabies in these settings, would also facilitate the success of control
293 interventions.^{81,147-149}

294 **Population-level control**

295 The strategy of individual case management has failed to appreciably reduce the transmission
296 of scabies in high-prevalence settings.^{6,150} Recent data from studies using MDA have led to
297 renewed interest in the potential of MDA to contribute to sustained population-level

298 control.^{151,152} Programs of mass treatment combined with additional screening and case
299 management in Panama and Australia (using permethrin)^{6,9,153} and the Solomon Islands
300 (using ivermectin)¹⁵⁴ considerably reduced scabies prevalence. Indirect evidence from
301 Zanzibar suggested a reduction in consultations and prescriptions for scabies following
302 annual MDA of ivermectin and albendazole for lymphatic filariasis^{155,156} but a study from a
303 lower prevalence setting in mainland Tanzania did not show a sustained effect.¹⁵⁷ However,
304 in lymphatic filariasis control programs, children under 5 years are not given ivermectin (or
305 any other agent active against scabies), which may explain ongoing transmission in this
306 context. The only controlled trial of community treatment published to date was conducted
307 in small, relatively isolated island populations in Fiji, where a single round of ivermectin-
308 based MDA reduced the prevalence of scabies by 94%, in comparison to the permethrin-
309 based MDA (62% reduction) and screen-and-refer arms (49% reduction).¹⁵⁸ These effects
310 have now been shown to be sustained up to 24 months post intervention.¹⁵⁹ The ivermectin-
311 based MDA intervention also resulted in a reduction of impetigo of 67% without adjunctive
312 mass antibiotic treatment. Further work in the Solomon Islands using ivermectin-based MDA
313 in a much larger population reported reductions in scabies prevalence of around 90%, and in
314 impetigo prevalence of around 75%.^{14,130} Conversely, ivermectin-based MDA for scabies in
315 northern Australia was not associated with a sustained reduction in prevalence.⁷⁹ The
316 different results observed in the Australian study may have been due to increased interactions
317 with surrounding untreated communities; lower baseline prevalence (4%, as compared to 32-
318 42% in the Fiji study); and transmission from untreated individuals with crusted scabies.

319 These studies set the scene for further investigation of the role of programmatic MDA in
320 scabies control. Priority future studies include investigation of whether a single dose of
321 ivermectin (as opposed to two doses, 7 to 14 days apart) is sufficiently effective as MDA for
322 scabies, and investigation of ivermectin-based MDA in other settings, including non-island
323 populations where population mobility may be greater. While existing MDA data suggest
324 effectiveness at high or very high population prevalence of 10 to 40%, the relative roles of
325 MDA and case management at lower prevalence, for example, less than 10%, have not yet
326 been adequately explored. Investigating the effect of MDA for scabies on complications such
327 as skin and soft tissue infection, sepsis and autoimmune sequelae will be important, but
328 require a large sample size and significant investment in infrastructure for active surveillance.
329 Studies of moxidectin-based MDA should also be prioritised, if initial individually
330 randomised clinical trials demonstrate efficacy.

331 Implementation research of integration of scabies control with other NTDs, particularly those
332 affecting the skin, has the potential to demonstrate cost-efficient delivery of multiple health
333 interventions.^{56,160} Initial studies could focus on understanding the impact of ivermectin-
334 based MDA for onchocerciasis and lymphatic filariasis on the prevalence of scabies in areas
335 that are scaling up treatment, as well as the effect of cessation of MDA in areas that are
336 scaling down treatment. There is concern that as ivermectin use for these programs is rolled
337 back in some countries, there could be a resurgence of scabies infestation, which may be a
338 major unintended consequence for communities. An additional research priority will be to
339 investigate the feasibility and impact of adding topical scabies treatment of young children to
340 existing ivermectin-based NTD programs. The possibility of developing a scabies vaccine has
341 been considered, although this approach is still at an early stage of development.^{43,161,162}

342 **Developing a global strategy**

343 Despite some deficiencies in the evidence for scabies control strategies, there is a need to
344 develop preliminary recommendations that can be implemented by countries wishing to
345 commence control measures, alongside pursuit of the research agenda described above. Initial
346 guidance is required on the threshold of scabies prevalence above which MDA could be
347 recommended, and other health system-related, geographic, socio-political or pragmatic
348 factors that might affect this decision. In lower-prevalence settings, intensified case
349 management strategies may be more appropriate. If MDA is to be utilised at large scale, then
350 guidance will be required on the control target, number and frequency of MDA rounds, and
351 monitoring and surveillance plan, including post-MDA surveillance, drawing on the lessons
352 from other NTDs.¹⁶³ This initial guidance should draw on the existing evidence-base, and—
353 acknowledging the limitations of current data—expert opinion and modelling work, with
354 plans made for guidance to be refined as further evidence becomes available. If sustained
355 control can be demonstrated, then it may be appropriate to consider the possibility of
356 elimination (interruption of transmission) at a national or regional level.

357 Once a mapping strategy is developed as part of a global control strategy, it will be possible
358 to estimate the at-risk population requiring ivermectin and permethrin within individual
359 countries and, with less certainty, at regional and global levels. Individual countries would be
360 able to develop control plans as part of broader NTD strategies, taking into consideration the
361 relative burden of scabies and other health issues.

362 It will be essential to advocate for access to affordable, quality-assured medications.
363 Ivermectin has been generously donated through the Mectizan Donation Program for
364 onchocerciasis and lymphatic filariasis in Africa and Latin America. This donation has
365 recently expanded for use in countries where onchocerciasis is not endemic, as part of the
366 IDA treatment strategy for lymphatic filariasis elimination.¹⁶⁴ However, it is unclear if such a
367 program could be extended to include scabies control as an indication. Although a donation
368 program would maximise the likelihood of achieving control, low-cost, high-quality generic
369 ivermectin may also be affordable in some settings. In addition to advocacy for donations,
370 manufacturers of generic ivermectin could be supported to apply for WHO pre-qualification.³
371 There is no precedent for a donation program for permethrin, and considerable amounts of it
372 would be required for treatment of individuals for whom ivermectin is contraindicated. The
373 licence holders of moxidectin, Medicines Development for Global Health, have committed to
374 providing moxidectin at an affordable price for scabies control in low- and middle-income
375 countries, if efficacy is demonstrated.¹¹⁶

376 **Conclusions**

377 Scabies is a common illness and major health issue affecting communities in many resource-
378 limited settings, and warrants public health intervention. There is strong evidence that
379 ivermectin-based MDA strategies can be highly effective in reducing the burden of scabies
380 and impetigo in at least some settings. Future research priorities include further defining the
381 burden of disease, developing standardised approaches to diagnosis and population burden
382 estimation, novel diagnostics and treatments, and evaluating large-scale community control
383 strategies. Interim guidance on scabies control is now required.

384

385 **Contributors**

386 D. Engelman and ACS conceived of the project. D. Engelman searched and reviewed the
387 literature, wrote the first draft of the manuscript, made revisions and prepared Figure 3. D.
388 Engelman, LR, MJW, JMK and ACS reviewed prevalence data for Figure 2. D. Engelman,
389 PTC, MM, AWS, JMK and ACS contributed to further development of the structure and
390 content. All authors reviewed drafts of the manuscript, provided comments and critical
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392

393 **Declaration of Interests**

394 Prof. Chosidow reports personal fees from Codexial and Zambon. All other authors declare
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396

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840 **Search strategy and selection criteria**

841 References for this review were identified through searches of PubMed for articles published
842 from January, 1990, to March, 2019, using the terms “scabies” and “*Sarcoptes scabiei*.”
843 Reference lists of identified manuscripts were reviewed to identify additional relevant
844 material. No language restrictions were imposed.

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849 **List of Acronyms**

850 DALY, disability-adjusted life year

851 ELISA, enzyme-linked immunosorbent assay

852 GBD, Global Burden of Disease

853 IACS, International Alliance for the Control of Scabies

854 IDA, ivermectin, diethylcarbamazine and albendazole

855 LMIC, low- and middle-income countries

856 NTD, neglected tropical disease

857 MDA, mass drug administration

858 US FDA, United States Food and Drug Administration

859 WHO, World Health Organization

860

861 **Panel 1. Key Research Questions**

862 Diagnosis

- 863 • What is the accuracy and reproducibility of diagnosis using the 2018 IACS Criteria?
- 864 • Can a limited skin examination protocol by non-expert health workers provide
- 865 acceptable accuracy for estimating prevalence?
- 866 • Can accurate skin-sample or blood tests be developed for scabies diagnosis?

867 Epidemiology and mapping

- 868 • What is the global burden of scabies? Which countries have the highest burdens of
- 869 scabies?
- 870 • What is the at-risk population living in highly-endemic settings?
- 871 • Are there identifiable risk factors for areas of high prevalence?
- 872 • What is the correlation between prevalence in school-attending children and the
- 873 community?

874 Transmission and complications

- 875 • What are the transmission dynamics of scabies?
- 876 • To what extent does crusted scabies drive transmission in highly endemic settings?
- 877 • What is the association between scabies and impetigo outside the Pacific region?

878 Social and economic

- 879 • What is the social burden of scabies as perceived and understood by affected
- 880 communities?
- 881 • What is the acceptability of MDA for scabies to affected communities?
- 882 • What approaches can effectively engage communities to support scabies control
- 883 initiatives?

884 Treatments

- 885 • Can ivermectin or other oral agents be safely administered to children of height < 90
- 886 cm, weight <15 kg or age <5 years?
- 887 • Are novel topical agents as effective, better tolerated or more affordable than
- 888 permethrin?
- 889 • What is the effectiveness of moxidectin for individual treatment and MDA for
- 890 scabies?

891 Mass drug administration for scabies

- 892 • What is the optimal dose and dosing strategy of ivermectin for MDA?
- 893 • What is the optimal interval between rounds of MDA?
- 894 • What is the impact of MDA for scabies on the burden of impetigo, severe bacterial
- 895 soft-tissue and systemic infections, glomerulonephritis and rheumatic heart disease?
- 896 • Under what conditions would MDA for scabies be cost-effective?
- 897 • How can ivermectin-based MDA for scabies be safely and effectively integrated
- 898 and/or co-administered with MDA for other NTDs?

899 Control strategy

- 900 • In what circumstances (threshold scabies prevalence or other factors) should MDA
- 901 and intensified case management strategies be used?
- 902 • If MDA is not being used, how can intensified case management be implemented?

- 903
- What are the effects of ivermectin-based MDA programs for other NTDs on scabies?
904 What happens to scabies prevalence when these programs cease?
 - What is the feasibility and effect of adding permethrin treatment of young children to
905 existing ivermectin-based MDA programs for other NTDs?
906
 - What, if any, environmental measures should be recommended?
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910 **Panel 2. Key Programmatic Issues**

911 Epidemiology

- 912 • Development of a protocol and training package for scabies mapping
- 913 • Mapping scabies prevalence using standardised methods, focusing on LMIC
- 914 • Integrated surveys with other NTD and health programs
- 915 • Surveillance strategies for potential outbreaks in high-risk settings
- 916 • Understanding high-burden groups within high-income settings

917

918 Population-level Control

- 919 • Interim guidance for public health control of scabies, including thresholds for starting
- 920 and stopping MDA, number and frequency of rounds, drugs and doses.
- 921 • Interim guidance on control of scabies outbreaks in institutions and communities
- 922 • Monitoring and evaluation strategy for impact of interventions on scabies
- 923 • Monitoring and evaluation strategy for impact of interventions on scabies
- 924 complications and other conditions.
- 925 • Monitoring for resistance

926

927 Strategy

- 928 • Define a global control strategy with targets
- 929 • Affordable and reliable access to oral and topical medications for treatment
- 930 • Ivermectin listing on WHO Essential Medicines List for scabies indication
- 931 • Integration with programs for other NTDs and other health programs
- 932 • Develop proposal for a future World Health Assembly resolution

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FIGURE LEGEND

Figure 1: Child's feet with skin manifestations of scabies infestation and secondary pyoderma

Photo courtesy Millicent Osti

Figure 2: Prevalence of scabies in children and adolescents younger than 19 years

Prevalence is shown at the country level, using available data from Romani *et al.*, 2015⁴ and updated with additional references.^{8,10-17} Subnational variation exists but is not represented in the map.

Figure 3: Primary and secondary effects of scabies infestation