

## **REBUTTAL LETTER – accompanying Dobigny & Morand REVISED v2**

Two recent critical papers for our own purpose (Gandy, 2021; Blasdell et al., 2022; Verrelli et al., 2022) were added to our review.

Review by [Eric Dumonteil](#), 25 May 2022 15:41

This is a nice review, well organized and presented, with clear recommendations for future directions of discussions and research. My only concern is the heavy focus on viruses and to a lesser extent bacteria. Although this is understandable, given their rapid evolutionary time scale that can favor their rapid emergence, it would be important to better include parasites in this discussion as urban habitats can also favor their evolution as well, even though this may be a slower process. It is also surprising that the section on arthropod vectors does not extend more on vectors that are already well adapted to urban environments and responsible for major disease burden (dengue, Zika, Chagas disease, etc...).

### Answer and associated modifications

We agree that zoonotic agents other than bacteria and viruses were poorly mentioned in our review. In order to fill this gap, three examples of worms of zoonotic importance (*Angiostrongylus cantonensis*, *Hymenolepis diminuta* and *H. nana*) in cities from Asia and Africa were mentioned in section 3.2, and a review on the situation in North American cities was quoted as well. In addition, the central role of pet and stray cats in the spreading of *Toxoplasma gondii* within urban environments was cited in section 3.1. Finally, the effects (actually, the rarity of knowledge about the effects) of urban environments on zoonotic pathogen evolutionary fate was discussed in a broad sense; so parasites are not excluded (see section 4). Altogether, this translated into five extra references focusing on non-bacterial and non-viral zoonotic pathogens (see reference list) which add to the already existing references on *Plasmodium*, *Trypanosoma*, etc.

As far as urban-adapted vectors are concerned, we agree with the reviewer that many vector-transmitted virus and parasites have been described and studied in cities for decades. This was already stated in section 3.4: « [...] many vectors of primary health importance show clear trends of adaptation to urban ecological conditions (e.g., *Anopheles* spp.: Azrag & Mohammed, 2018; Takken & Lindsay, 2019; *Aedes* spp.: Wilke et al., 2020), sometimes taking advantage of remnant forests, urban parks and increasing city greenings (e.g. ticks and tick-borne diseases: Lydecker et al., 2019; Heylen et al., 2019). Accordingly, several studies have clearly pointed towards the existence of urban zoonotic cycles of vector-transmitted pathogens, thus suggesting increasing city-specific infectious risks (e.g., tick-borne *Borrelia*: Reye et al., 2010; mosquito-transmitted Zika virus: Musso & Gubler, 2016). ». Nevertheless, some references were added to this sentence in order to reinforce this statement: « [...] many vectors of primary health importance show clear trends of adaptation to urban ecological conditions (e.g., Triatomine bugs: Parra-Henao et al., 2021; *Anopheles* spp.: Azrag & Mohammed, 2018; Takken & Lindsay, 2019; *Aedes* spp.: Wilke et al., 2020), sometimes taking advantage of remnant forests, urban parks and increasing city greenings (e.g. ticks and tick-borne diseases: Lydecker et al., 2019; Heylen et al., 2019; typhus-transmitting chiggers: Wulandary et al., 2021; *Aedes* spp.: Huynh & Minakawa, 2022). Accordingly, several studies have clearly pointed towards the existence of urban zoonotic cycles of vector-transmitted pathogens, thus suggesting increasing city-specific infectious risks (e.g., tick-borne *Borrelia*: Reye et al., 2010; mosquito-transmitted Zika virus: Musso & Gubler, 2016; triatomine-borne

*Trypanosoma cruzi*: Dye-Braumuller et al., 2019). ». This implied the addition of four extra references (see reference list).

### Review by anonymous reviewer, 13 May 2022 09:29

This review aims to draw readers' attention to the importance of urban ecosystems on disease emergence from wildlife

I found this paper very timely. The recent Covid outbreak attracted the attention on wildlife-human new interfaces due to overexploitation of agro systems in many tropical countries, but it is true that cities (including peri-urban areas) and their specific conditions were overlooked as potential important places of zoonotic emergence. Yet, the plague outbreak in middle-age in Europe was amplified in cities.

I have a number of comments, but I have to say that none of them jeopardizes the publication of this paper, which seems important to me.

#### Answer and associated modifications

1- The paper is about emergence of diseases in humans. I think that this should be emphasized in the general introduction, because there are also potentials for cities to be important places for emergence and spread of diseases staying in the animal compartment (e.g. avian influenza)

This was done accordingly (see Abstract, and two instances in the Introduction).

2- P. 4, L. 5 and others references to figures. Figures 1 and 2 are of poor quality in this version. Is it possible to improve this quality? Else, P. 12, there is a reference to Figure 3, but there is no figure 3 in the version I have access to.

High-resolution figures 1 and 2 were provided.  
The reference to Figure 3 was a mistake. It has been deleted.

3- P. 9 L. 20. I would add a sentence of general conclusion for summarizing this important chapter (high animal densities + high prevalence + frequent contacts with humans = high probability of spillover)

This was done accordingly (see end of section 3.2 : « Altogether, these studies illustrate how abundant pathogen-carrying wildlife, especially small flying and terrestrial mammals, may be in cities where human density reaches its maximum, thus setting the scene for billions of everyday wildlife-human interactions, hence spill-over opportunities. »).

4- P. 10 L. 17-20. At least, even if not the source, the market here played a role in the amplification of epidemics.

We agree with this remark and have made it clearer in our revised text: « In addition, many urban markets group living wild animals, thus probably greatly enhancing the chances of infectious pathogens spillover as well as the number of persons potentially involved, thus favoring epidemics early stages. » (see section 3.3).

5- P. 12, L. 8. To hammer the nail, I would begin the sentence by something like “Importantly, even before human contamination”...

This was added accordingly (see section 4, second paragraph).

6- P. 12 or somewhere else. Maybe it would be worth adding a paragraph on cities as ideal socio-ecosystems for emergence of diseases carrying resistance to antibiotics (which would add a problem to the problem). Antibiotic resistance is noted in the “evolutionary consequences” (P. 13 after L. 23), with the possibility for recombination between microbe strains, but I think that cities, because to high level of pollution and overconsumption of antibiotics may also provide direct strong selective pressures for resistance selection, e.g.

Rilstone, V; Vignale, L; (...); Champagne, P. The role of antibiotics and heavy metals on the development, promotion, and dissemination of antimicrobial resistance in drinking water biofilms. CHEMOSPHERE 282, DOI 10.1016/j.chemosphere.2021.131048

Buelow, E; Ploy, MC and Dagot, C Role of pollution on the selection of antibiotic resistance and bacterial pathogens in the environment. CURRENT OPINION IN MICROBIOLOGY 64 , pp.117-124, DOI: 10.1016/j.mib.2021.10.005

We concede that this aspect was missing. A sentence has now been added to section 4 in order to take it into account : « Following overconsumption and subsequent release of antibiotics in the urban environment (Buelow et al., 2021), repeated exposure of pet and domestic animals as well as urban wildlife to a wide spectrum of antibacterial molecules is highly probable, and would greatly contribute to antibio-resistance evolution. ».

7- P. 15, L. 13. About the heterogeneity of urban socio-environment. Well, opposing urban vs. non-urban also suppose that non-urban is also homogeneous, which is obviously not the case!

We agree with this comment –which, however, does not call for any modification here.

8- P. 15, L. 26 and after. Are these proposals specific to urban areas?

Although our concern is specifically about cities here, these proposals indeed remain valuable for any type of socio-ecosystems. Accordingly, our text was slightly reworded: « From a surveillance perspective (in cities, but also in other socio-environments), human sciences should take the scene early in the process of building One Health actions. » (see section 5, beginning of fourth paragraph).

9- P. 17, L. 6-17. Perhaps it would be interesting to compare these recommendations with those for invasive species, in order to draw inspiration from them. E.g. (among many others)

Reaser, JK ; Burgiel, SW (...); Burgos-Rodriguez, J The early detection of and rapid response (EDRR) to invasive species: a conceptual framework and federal capacities assessment. BIOLOGICAL INVASIONS, Volume22, Issue1, Page1-19 DOI10.1007/s10530-019-02156-w

Miralles, L ; Ibabe, A (...);Borrell, YJ "If You Know the Enemy and Know Yourself": Addressing the Problem of Biological Invasions in Ports Through a New NIS Invasion Threat

We agree that bioinvasion management could be an inspiring source for the design of early detection and rapid response to zoonotic emergence. Our text was modified as following : « It could be interested to capitalize on concepts and approaches developed for biological invasion management (e.g., see the special issue in Biological Invasions journal about “Early Detection and Rapid Response” of invasive organisms, eds. Meyerson, A. & Simberloff, D., 2020). For instance, collaborative platforms of surveillance managed jointly by academic, institutional and operational stakeholders could be implemented within transport stations, ports and seaports (e.g. Port Platform of Environmental Surveillance currently settled in Cotonou seaport, Benin; Adamjy et al., 2020). ». (see end of the sixth paragraph of section 5).

10- P. 18, L. 16. This also implies sharing the knowledge rapidly, without any political ulterior motive... (Utopia, I'm afraid)

We agree that the issue of rapid transmission of knowledge from local communities to health authorities in order to launch higher-level responses. In order to take this point into account, a sentence was added at the end of the seventh paragraph of section 5 : « It also raises the issue of rapid sharing of knowledge from the communities to the Health authorities in charge, whoever they might be, in order to trigger immediate coordinated higher-level responses. ».

#### Review by [Nicole L. Gottdenker](#), 20 Jun 2022 20:14

This is a review-concept paper of zoonotic disease emergence in urban systems there are many of these kind of reviews in the literature, but this one has some additional novel contributions. The review overlooks some recent synthetic reviews discussing socioecological factors related to urbanization and zoonotic disease emergence (Combs et al. 2021. <https://doi.org/10.1111/gcb.16033>). The review is among many that discuss urbanization and zoonotic disease. Comments regarding some details and larger issues in the paper are as follows:

Please note that there are many English/syntax errors and I am not reading the paper to capture and correct all of these-Actually, the paper seems very 'rushed' the way it has been written and merits some significant editing- will put some of the corrections below.

The whole manuscript was been rechecked by a native English speaker colleague.

I think that an overall diagram summarizing the papers key points would be useful for the reader and a good synthesis of the material. I suggest adding one (a diagram or illustration that serves as a synthesis and summary of article's key points).

We thank the reviewer for this valuable suggestion. Accordingly, we have produced a graphical abstract summarizing the main ideas discussed in our paper. This synthetic figure now replaces the previous Figure 2 – that the reviewer has suggested to remove (see below).

abstract:

line 18-19 Delete

'(e.g., better description of extended urban socio-ecosystems in urban health ecology studies; truly evaluated interventional researches') not necessary

This was done accordingly.

line 19- I would use another term instead of 'slum' even if the UN and other agencies use it- it is a loaded term and has a heavy bias associated with it (see Gilbert, A., 2007. "The return of the slum: does language matter?". International Journal of Urban and Regional Research, 31(4), pp.697-713.)

We agree that the common sense of « slum » is heavily loaded and may be controversial in some instances. In order to address this semantic point, and following the recommendation of an urban geographer colleague, it was changed into « informal settlement » in all instances.

First paragraph of the first paragraph of the introduction.

lines 23-24 (and also the end of the first paragraph of the it there are studies on per-urba, urban and suburban areas on zoonotic diseases (see studies on rabies in Canada, leptospirosis and other diseases in New Orleans, leptospirosis in Rio de Janeiro, urban Chagas in Venezuela).

We agree that quite an important amount of studies exist on urban zoonoses (including ours) – and leptospirosis, rabies and Chagas diseases in urban contexts were all mentioned at some points of our manuscript and reference list. However, the point of the introduction was to put forward the scarcity of reviews (even in high-standard journals) focusing on cities, relative to the much more numerous ones pointing towards zoonotic risk associated with agro-ecosystems and forests.

However, in order to take this remark into account, the sentence was slightly reworded into: « Yet, despite existing studies on urban-associated zoonoses (see below), we believe that further attention should be paid to urban, peri-urban and sub-urban areas where massive though not fully evaluated contacts between wildlife, domestic animal and inhabitants occur on an everyday basis. ». (see Introduction).

introduction

line 16- change 'many researches' to 'much research'

This was modified accordingly.

p. 4 line 20, delete - 'Thus, whatever this is good news or not'

This was deleted accordingly.

p. 5- change 'apprehension' to 'comprehension'

This was done accordingly.

The section in page 5 'Cities as places for millions of close animal-human interactions ' makes a very good point about some cities being close to a lot of biodiversity or zoonoses and merits

a bit more development of some specific examples of this point you are making (examples of some emergent diseases and these biodiverse urban locations.

We also agree that this is one of the main point of our paper. This is why it is already seven pages long (out of seventeen, making it >40% of the total length of the whole manuscript). Note that at least 29 cities / urban contexts (4 from South American, 2 from North America, 3 from Asia, 1 from Australia and 13 from Africa) and >20 different zoonotic pathogens (>11 viruses, 3 helminths, 1 protozoa and 6 bacteria) are mentioned at least once within this particular section. Close to 100 references are also cited. We are afraid that adding further examples would make this section 3 and the reference list significantly longer without bringing much argument. This is why we choose not to accumulate new examples/references here.

section on pets and domestic animals-

again, p. 5 line 28- please use another word other than 'slums'

See above our rebuttal on this particular point.

p. 5 line 29- change 'owner' to 'owners'

This was done accordingly.

In addition to the section on 'pets and domestic animals', I suggest adding a paragraph about stray animals in urban areas (dogs and cats), some suggestions include feral cats and urbanization and disease in Seoul 'Hwang et al. 2018, PeerJ, 6, e4988. <https://doi.org/10.7717/peerj.4988>', urban rabies in peru- De la Puente-León, M., Levy, M. Z., Toledo, A. M., Recuenco, S., Shinnick, J., & Castillo-Neyra, R. (2020). Spatial Inequality Hides the Burden of Dog Bites and the Risk of Dog-Mediated Human Rabies. *The American journal of tropical medicine and hygiene*, 103(3), 1247–1257.).

We agree with the reviewer that this point deserves to be put forward. This is the reason why, in addition to the case of cats and toxoplasmosis (see above, and section 3.1), we have added a sentence and two references to quote the case of urban free-roaming dogs involved in rabies circulation : « Stray dogs may reach very large numbers in some urban and peri-urban areas, thus sometimes greatly contributing to rabies virus circulation and transmission within cities (e.g., Tenzin et al., 2015; Castillo-Neyra et al., 2017). » (see beginning of section 3.1).

p. 6 line 3, change 'death occur' to 'deaths occur'

This was done accordingly.

p. 6 line 8, omit 'were recently demonstrated to'

This was done accordingly.

p. 6 line 16 the sentence that urban wildlife 'shelter an overall higher pathogen richness than their non-urban counterparts' is not always/universally true, but this can be context-dependent.

In order to specify that this is a trend obtained from a meta-analysis, the sentence was slightly reworded into: « [...] a recent meta-analysis suggests that wild urban-adapted mammal species tend to shelter an overall higher pathogen richness than their non-urban counterparts (Albery et al., 2021). ».

p. 6 lines 22-23- the section of this sentence needs to be rephrased for clarity: ' Many testimonies (e.g., Barkham, 2017) demonstrate that 22 peri-urban zones, when not core cities are now regularly visited by sometimes large and unexpected 23 animals: '

This sentence was reshaped and now reads: « Many records (e.g., Barkham, 2017) demonstrate that sometimes large and unexpected animals regularly visit peri-urban zones, when not core cities: [...] ».

p. 7 line 6 ' very large size' change to 'large population sizes'

The sentence was reworded into : « [...] namely rodents and bats, whose urban communities may display very high densities and very large population size [...]. ».

also in the section on wild animals perhaps mentioning urban rabies and raccons would add to this discussion- again please use another word for slums throughout the manuscript.

The example of urban-adaptable raccoons was added to this section : « Raccoons, reservoirs for rabies virus, also display great eco-ethological adaptation to contrasted urban landscapes and resource availability levels, thus allowing them to occur throughout some North American cities (Gross et al., 2012). ».

See above for the use of « slum(s) » (it was systematically changed into « informal settlement(s) »).

p. 9- the discussion on laboratory escape is very interesting- perhaps mentioning that one of the SARS cov-2 unproven hypothesis includes lab escape. Regardless, this section should be its own subsection separate from selling animals in marketplaces.

Although we agree lab escapees are an important point in terms of spillover risk and subsequent epidemics, we believe this section is quite short to be a subsection on its own. This is the reason why we left it under the larger heading « captive animals », even though it makes an independent paragraph.

The SARS-Cov-2 case is now briefly mentioned (with caution) in the revised version: « Among other hypotheses, a lab-escapee as a possible origin for the ongoing Covid-19 pandemics remains to be fully investigated (Harrison & Sachs, 2022).».

in Section 3.3, please do not use the term 'bush meat' or 'wet market' perhaps just change the terms 'wildlife meat commerce'. Can you change 'wet market' to 'animal meat market' ?= Wet market came from a direct mandarin translation, so perhaps just using the term 'animal meat/product market' is better.

In order to address this issue, « bushmeat » was modified into « wildlife meat », and « wet market » was modified into « wildlife meat market » (see section 3.3).

The last section on cities as incubators for 'evolutionary novelties' I think brings up some interesting points but needs some cohesion with evolutionary theory or processes (perhaps organizing paragraphs in this section in terms of evolutionary processes (See Gluckman et al. 2011- *Evol Appl.* 2011 Mar; 4(2): 249–263.).

p. 13-This page has a couple of paragraphs that don't fit under the evolutionary novelties heading and should have their own subsection, perhaps something like 'Cities as transportation hubs for pathogen movement and exchange'

and then the next paragraph have another subsection

'Impact of urbanization on microbial interactions'

We do not fully agree with this remark on the shape (not the content) of this section. As explained in our text and agreed by the reviewer herself, cities are important transportation hubs, thus indeed playing a particular role in reservoir, vector and microbe dissemination. However, we further advocate that, by essence, such hubs may also favour either new host-parasite associations, or new microbial contacts, hence strains/species admixture and, *in fine*, new pathogens dynamics and emergence. In such a context, it appears that spatial dissemination is tightly linked to pathogen and pathogen dynamics evolution, and we believe they should be considered as different steps of the same process – pathosystem reshuffling and subsequent evolution.

p. 14 line 12- change 'repeated animal-human transmission' to 'iteration of animal-human human-animal transmission events

We agree this wording is more pertinent. The sentence was thus changed accordingly.

p. 14 line 24- change 'researches are' to 'research is'

This was done accordingly.

p. 14 line 32- change 'researches' to 'research'

This was done accordingly.

Can you define briefly 'riposte' as used on p. 15 and 16?

We concede that « riposte » is incorrect in English – not the exact same meaning than in French. The appropriate word should be « response ». As a consequence, « riposte » was modified into « response » in the four instances where it was initially used.

p. 18- change- 'trans sectorial- to 'trans disciplinary'

This was done accordingly.

p. 18- do you know of any examples of centers of excellence in ecology and health research and training?'



We are aware of only some rare examples. Some of them are quoted in our revised text which now reads: « Accordingly, the creation of Centers (or Networks) of Excellence in Ecology and Health Research and Training housed in regional universities and/or research institutes had already been advocated more than fifteen years ago (Patz et al., 2004); unfortunately, to our knowledge, they are still rare (e.g., One Health Center of Excellence, University of Florida, USA; One Health Frontier Graduate School of Excellence, Hokkaido University, Japan; One Health Research Center of Excellence for Research and Training, Sun Yat-sen University, Guangzhou, China; One Health European Joint Program, European Union network). ».

The 'call for some actions' section is a bit 'rambling' perhaps shortening or significantly editing this section would increase the paper's clarity- it is a very broad paper.

In order to address the reviewer's point and to delineate better the last section 5, we have organized it into new sub-sections dealing with the following items: a better understanding of pathogen evolution at the animal-human interface within extended urban socio-ecosystems (5.1), from response to epidemics towards densified surveillance and prevention networks (5.2), a special role for local community-based networks (5.3), wide-scale empowerment on the One Health concept (5.4) and urban management and poverty reduction (5.5).

In addition, several sentences have been removed (see section 5), thus representing a ~15 lines shortening.

I am not sure how much the Figure 2 reprint is useful for this study and maybe could be replaced by the larger more synthetic diagram that I suggested.

As suggested by the reviewer, we have now replaced the previous Figure 2 by a new Figure 2. The latter one now corresponds to a graphical abstract summarizing the main ideas discussed in our manuscript.